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MATURITY*

Presidential Address

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IN THE lives of societies as in lives of men, growth and development and change come upon us almost without notice; only a few years stand out in our memories as milestones dividing the old from the new, and it is for us to recognize them and their importance.

We have reached the twenty-first milestone of an organization devoted to "the furthering of interest and advancement of obstetrics and gynecology," so let us pause to review our accomplishments and consider our future course.

On May 21, 1929, at the suggestion of Dr. Palmer Findley (Omaha), there met in his room at the Hotel Chamberlin-Vanderbilt at Old Point Comfort, Va., the following individuals: Dr. Palmer Findley, Omaha, Neb., Dr. Fred Taussig, St. Louis, Mo., Dr. Carey Culbertson, Chicago, Ill., Dr. Fred L. Adair, Minneapolis, Minn., Dr. E. L. King, New Orleans, La., Dr. John W. Harris, Madison, Wis., and Dr. E. D. Plass, Iowa City, Iowa.

The discussion revolved around the organization of an association of obstetricians and gynecologists in the Middle West for the purpose of stimulating the younger men in the specialty, who might otherwise have no reasonable outlet for the exchange of ideas and for their investigative results. It was agreed to canvass the states bordering on the Mississippi River for available

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members, and the area was divided into sections and men were assigned to these sections. The list of names of qualified and interested physicians was to be forwarded to the temporary chairman not later than Oct. 1, 1929.

The organizational meeting of the Executive Committee was held in St. Louis, Mo., on Nov. 22 and 23, 1929. The program committee, with Dr. Taussig as chairman and Dr. Findley working with him, arranged to have morning clinics and afternoon symposiums to be held in St. Louis on Dec. 6 and 7, 1929.

It was agreed that no one should be eligible for membership in the society until at least five years after graduation, and his major interest must be in obstetrics and gynecology. Members were to be selected from only those states bordering on the Mississippi and Missouri Rivers ond the Gulf of Mexico. The new organization was to be called "The Central Association of Obstetricians and Gynecologists."

The following temporary officers were elected:

Dr. Palmer Findley, Omaha, Chairman
Dr. E. D. Plass, Iowa City, Secretary

The first annual meeting took place in St. Louis, Dec. 6 and 7, 1929, together with the St. Louis Gynecological Society, directed by Dr. Fred Taussig. After a very successful first day, and following the dinner at the University Club in the evening, a Constitution and By-laws were enacted at the business meeting. The total registration of this first meeting was more than 123, the majority of whom became charter members. Officers for the ensuing year were elected as follows:

Dr. Palmer Findley, Omaha, President
Dr. E. L. King, New Orleans, Vice-President
Dr. E. D. Plass, Iowa City, Secretary and Treasurer

Executive Committee:

Dr. Carl Henry Davis, Milwaukee
Dr. Fred H. Falls, Chicago
Dr. P. W. Tooms, Memphis

From such a wonderful heritage, with excellent prenatal care, with birth through natural channels without even an episiotomy, this new organization could expect only to grow, and flourish with abundant fruition.

The organization of the society was followed by great success. It was voted to distribute President Findley's address, "The Teaching of Obstetrics and Maternal Mortality," to 1,500 people, all of whom were interested in teaching obstetrics and pediatrics, or were deans of universities in the United States and Canada.

The AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY became the official organ for publications of the society. The paid-up membership in 1930 was 137 members, and the financial status was satisfactory.

The American Board of Obstetrics and Gynecology was founded Oct. 15, 1930. Two of the charter members of the Central Association were on the original nine-member Board of Obstetrics and Gynecology.

The second annual meeting was held at Excelsior Springs, Mo., in October of 1930, in conjunction with the Kansas City Clinical Society in Kansas City. Sixty-five members were present, and 1,000 were in attendance at this meeting, which was beyond all expectation. It was envisioned that if each physician present had contacts with 1,000 individuals in practice, the doctrine of more conservative obstetrics and gynecology should reach directly or indirectly at least one million people. This shows the possible magnitude of the combined efforts of the society.

The papers at this meeting were of high scientific caliber, discussions were lively and to the point, with many young people participating. In the executive session the following decisions were reached:

1. Requirements for membership were established for active, emeritus, and honorary members.
2. The retiring president should continue as a member of the Executive Committee for one year after his term of office.
3. Physicians in all states operating on Central Standard Time (as designated by the United States Department of Commerce) might be admitted to membership, if they met the requirements in obstetrics and gynecology.

The Association's first Prize Award of $100.00 was given to Dr. E. D. Plass for "Monilia Vulvovaginitis."

The third annual meeting was held on Oct. 28, 1931, in Chicago, in joint session with the Chicago Gynecological Society. Seventy-two members were present with 99 guests. Discussion revolved around the White House Conference proceedings as related to obstetrics.

At this time the requirement that members should come from states bordering on the Mississippi and Missouri Rivers and the Gulf of Mexico or from those operating under Central Standard Time was changed, so that an applicant actually in attendance at the annual meeting when his name was proposed should be eligible for consideration. By the time of the third meeting there were already 170 members. The membership was limited at first to 250.

The fourth annual meeting was held at the Peabody Hotel in Memphis on Sept. 15, 16, and 17, 1932. New membership lists and the Constitution and By-laws were finally adopted as corrected. The membership consisted of active, life, and honorary members. The membership limit has necessarily been modified three times.

The development of this prodigy was well beyond that of a normal 3-year-old. Though this year was at the peak of the depression, in the warmth of southern hospitality, it grew rapidly in strength, self-confidence, and independence. For the first time the Constitution and By-laws were mailed to the 189 members. In August a newsletter was mailed, and in September the final programs were mailed to all members and applicants, as well as to the members of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. This established another precedent which has been partially maintained to the present.

The second Association Prize Award for the best scientific contribution was given to Dr. Ralph A. Reis, Chicago, for "Traumatic Rupture of the Symphysis Pubis During Spontaneous Labor."

In 1933, the meeting was held in Milwaukee, with 81 members in attendance and 89 guests. There was the usual wide range of essays and active discussions followed. The warm welcome extended to the guests has frequently resulted in larger guest attendance than membership attendance.

The Central Association of Obstetricians and Gynecologists cooperated with the American Gynecological Society and the American Surgical Society in the National Conference on Nomenclature of Disease to formulate a classification of operations.

In an endeavor to keep this a young man's organization, Section II, Article 3, was changed as follows: Members who are beyond 55 and who have been members for over five years may apply for emeritus membership to allow younger men active membership.

Representatives were sent to the National Committee on Maternal Health. The annual business meeting was changed from the night of the banquet to the afternoon of the second day. Full notes of discussions were kept and filed for the first time. Two newsletters and a program were sent out during the year.

In 1934 the meeting was held in New Orleans. There were 72 members, 35 guests, and 54 ladies present. This was a joint meeting with the New Orleans Gynecological and Obstetrical Society. A letter telling of the Association's progress and a new revised Constitution and By-laws were sent to each member. Active members were required to attend one meeting every three years and to pay their dues annually. Otherwise they would automatically be dropped from membership. The meeting was very successful, and, although this was in the time of a depression, the spirit of the Association was not daunted. A contribution of $100.00 was given to the work of the American Committee on Maternal Welfare.

The seventh annual meeting was in Omaha in 1935. There were 206 members. The president sent a personal invitation to every member. The financial condition remained satisfactory. From this time on newsletters were sent out twice yearly, and the program was sent out a month before the date of the meeting. At this meeting a study of clinical affairs by questionnaire was begun, which lasted four years, with a study of cesarean section, ectopic pregnancy, abortions, and chronic cervicitis.

The requirements for the Prize Award Thesis were changed and enforced:

1. Not to have been previously published or read before another society.
2. To be submitted six weeks before the annual meeting at which it is to be presented.
3. To be submitted in triplicate, without identification or signatures, and be selected by a secret committee of three.
4. To be read at the meeting of the Central Association.

The organization met with the Detroit Obstetrical and Gynecological Society in 1936. There were 220 members officially in good standing; 4 honorary members, and 7 emeritus members. The Central Association had begun to reach its full stature as an adolescent. Mother's classes were formed in cooperation with the local Maternal Welfare Committee of the state medical societies.

The American Congress on Obstetrics and Gynecology was discussed, and originated partially from the ideas of the Central Association. At first a $2,500.00 revolving fund was set up for the Congress, which first met in Cleveland, and for each succeeding Congress, but for the Fifth Congress an outright gift was made.

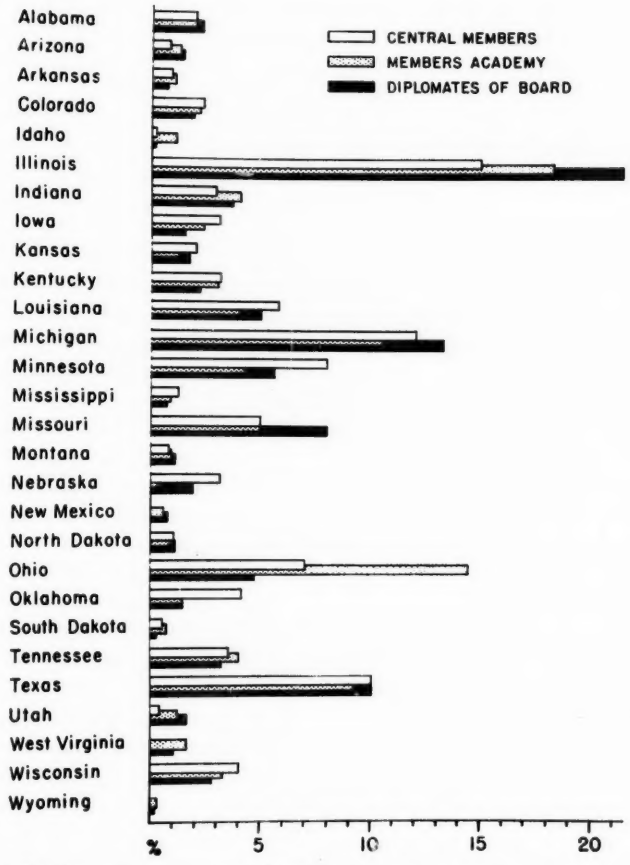

Fig. 1.—Shows distribution of society membership by states in the Central Association area.

It was decided in Executive Committee that twenty-eight states were to be included in the central section, and the membership was raised to 300 (Fig. 1).

The Central Association of Obstetricians and Gynecologists took its first step in sponsoring other organizations:

1. Committee on Maternal Welfare, $100.00
2. Committee on Clinical Affairs, $100.00
3. Committtee on American Congress, $2,500.00 (revolving fund)

So with each annual meeting the growth, strength, and influence of the organization continued to increase. The meetings were filled with enthusiasm. Excellent papers were presented and were well discussed. Guests were always extended a warm welcome. The finances of the organization have always been good. One problem was apparent early, that the demands on the society were greater than could be carried out with a limited membership. Often there were 60 to 80 well-qualified applications for membership with only 5 to 10 vacancies.

The importance of an organization lies in the qualities of the mind and heart. Our founders implanted qualities of intellect, insight, and idealism that have grown with the years.

The officers have always been selected from different sections representing the geographical confines of the Association, and the meetings are held with the plan of rotating through the whole central area, from Omaha to Dallas, and back to Minneapolis and then New Orleans. Meetings have been held twice in seven of the cities of the central states—Chicago, St. Louis, Memphis, New Orleans, Kansas City, Milwaukee, and Detroit. One of the most pleasant experiences is that the welcome on our return is greater than at the first meeting. No expense is necessarily incurred by the local committees. Local obstetrical and gynecological societies take one day or one afternoon as a part of the meeting, and there is always a great stimulus to the local society.

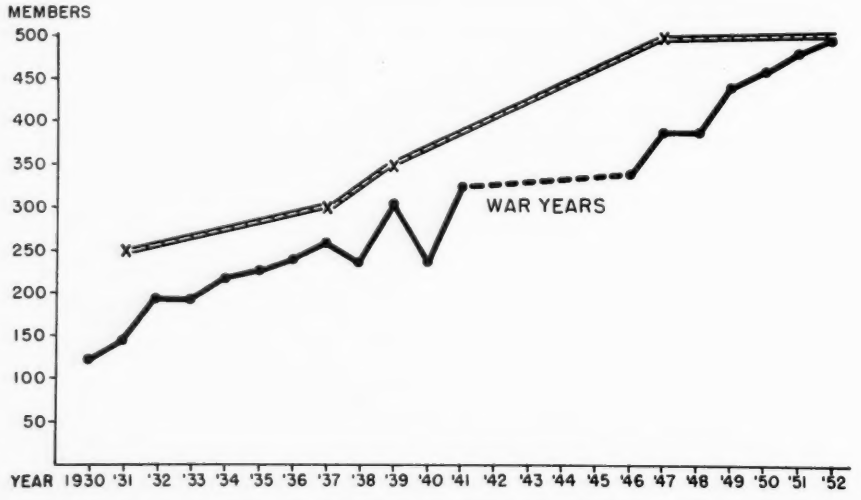

Fig. 2.—Central's growth. Solid line indicates number of members in attendance at each meeting. Broken line (X) shows limitation of members at different periods.

In 1938 the membership limit was raised to 350. The annual meetings were stimulating and friendly. The whole mechanism of the society was by now functioning extremely well. Good papers on a wide range of subjects were discussed, and there was great personal pride in the organization. Throughout the years the sincere welcome and large attendance of guests at the meetings not only enlarged the influence of the society, but permitted many more to profit by the meetings.

In 1940 the annual meeting was held in Indianapolis, and a special program was put on for the tenth anniversary. All the living past presidents were present, and a review of progress was given by Dr. E. D. Plass. I quote:

"Even at the age of 10 years it has more than fulfilled the expectations of the small group who watched over its fetal development and whose expressed purpose was to nurture an organization 'for the purpose of stimulating particularly the younger men in the specialty who might otherwise have no reasonable outlet for their investigative results.'

"There is not sufficient time to review the achievements of the organization, nor to attempt to prophesy its future, but its heredity was admirable, its prenatal influence excellent, and its birth natural and uncomplicated. There is every reason for hoping that its influence will continue to grow and that irrespective of the changes which may come in obstetrics and gynecology, the Central Association will lead the way."

The next meeting, held in New Orleans in 1941, was also very successful. The following year the cloud of World War II hovered over the world, and on June 23, 1942, after a vote by mail of 227 out of 292 favoring discontinuance of the annual meetings for the duration of the war, President John H. Moore, by telephone hookup of the Executive Committee, officially announced that the meetings of the Association would be discontinued for the duration of the war.

The Executive Committee held annual meetings in Chicago each November from 1942 through 1945. At these meetings the business at hand was carried on, and plans for the future of the society were formulated.

In October of 1940, at the suggestion of Dr. Carl P. Huber, a gavel was made from twenty-eight pieces of wood from each of the states represented. The gavel was made up by Dr. William F. Mengert and was presented to the Association in 1943.

The first postwar meeting was held in Chicago on Nov. 19, 20, and 21, 1946. There were officially 297 members and 109 guests. Eighteen essays were presented, and two Prize Awards were given. Through this time the records showed 75 members serving in the Armed Forces, 44 in the Army, 31 in the Navy. No casualties were reported.

This meeting revealed that the years of war had not dampened the spirit and fellowship of the Central Association. The usual donations were made, to the National Society for Medical Research, the National Federation of Obstetric-Gynecologic Societies, and the Third American Congress on Obstetrics and Gynecology.

The Association also endorsed the American Academy of Pediatrics' Study of Fetal Deformities in Connection with Certain Communicable Diseases.

During the past years there have been other interesting changes. The first secretary-treasurer was Dr. E. D. Plass, Iowa City; he was followed in 1933 by Dr. Ralph Reis, Chicago; in 1937, by Dr. William F. Mengert, Dallas; by Mr. Karl Richardson as executive secretary in 1945-1946; and by Dr. John Brewer, Chicago, in 1946. In 1947, Mr. Donald F. Richardson became the permanent Executive Secretary. Since then, in the past three years, Dr. Harold L. Gainey, Kansas City, has been the secretary-treasurer with Mr. Richardson as Executive Secretary.

There have been seventeen Prize Award papers given during these years, and it is of interest to note the variety and scope of these papers. Eighteen papers are usually read at each meeting, including the presidential address. These are distributed between obstetrical and gynecological problems.

On Oct. 23, 24, and 25, 1947, the meeting was held in Louisville, Ky. There were officially 325 active members, 67 life members, and 8 honorary members. Dues were raised to $10.00 per year, and were to be paid by all active members in or out of the Armed Forces. The first attempt at the division of the society was made, but was not passed. Dues were paid to the National Federation of Obstetric-Gynecologic Societies. It was voted that no certification of membership was to be given to each member, and an annual transaction volume was not to be printed because of the excessive cost and the availability of the material in the "Gray Journal" and reprints. A committee was appointed to work with other gynecological societies to establish a national pathological registry. The membership was raised to 500, and 87 new members were taken in at this time. Two hundred dollars was given to the National Society for Medical Research. At this time there were inaugurated the sectional round table discussions in the afternoon, which have grown rapidly.

One of the most vital processes in the maintenance of the high quality of membership has been the careful selection of the applicants by the Membership Committee, with regard to location, work done, training, specialization, papers written, age, personality, etc. These applicants are graded by three members of the Membership Committee and the names are then presented to the Executive Committee and are taken up individually. Here again each applicant is evaluated objectively and individually. The method of grading is as follows:

Under 55 years of age	1 point
Years of special training:	
Two years	1 point
Three years	2 points
Four years or more	3 points
Diplomate of American Board of Obstetrics and Gynecology	3 points
Teaching position in accredited Medical School	1 point
Number of publications	1 point

Two points place the applicant in Group 4
Three to five points place the applicant in Group 3
Five to eight points place the applicant in Group 2
Eight or more points place the applicant in Group 1

If the applicant does not limit his practice he is not to be considered. A file is started for each applicant the year he originally applies. The number of applications, the age of the individual, etc., are also considered.

In 1948 the meeting was in Denver, with 211 members, 208 guests, 75 life members, and 9 honorary members present. In addition to the usual annual

donations and one to the Fourth American Congress, it was voted also to help subsidize the publication of the autobiography of Dr. Robert O. Meyer. Awards were given for clinical and investigative work.

The rapid increase in the past year in the number of new members noticeably changed the personality of the Central Association. The friendly, close comradeship changed to surging, ambitious aggressiveness.

The 1949 meeting was held in Oklahoma City. Newsletters were sent out three times during the year, and the roster was mailed. No Prize Awards were given. There were officially 428 members, 81 life members, 10 honorary members. It was voted to give one $250.00 Prize Award on the clinical or investigative work instead of two awards. The constitution was changed so as not to require a new member to be present at the meeting when he was voted on, but to be present at the next meeting. A gift of $250.00 was given to start a registry in gynecological pathology. A grant was given to the International and Fourth American Congress in New York. There was a discussion of the dues for the National Federation of Obstetric-Gynecologic Societies and the Central Association's membership in the Federation. The Litzenberg Memorial Committee was formed. A committee was also appointed to help raise funds for loans to establish the pathology registry.

At all times the Central Association was pressed to enlarge and take in more members. In 1932, shortly after the Association was founded, there were 102 Board members in the section, and in 1952 this had increased to 1,303. Likewise, membership in the American College of Surgeons has grown to 7,743. In 1952 there were 92,387 doctors, 24,072 specialists, and 33,957 in limited practice. Yet there were few organizations where they could meet to converse or exchange ideas. In 1948 restlessness set in, and petitions were made requesting a vote as to whether or not to divide the society between North and South. In 1949, Dr. William F. Mengert, with the organization really at the crossroads, proposed to change the Central Association of Obstetricians and Gynecologists to a national organization:

"Mr. President, as an immediate past president of the Central Association and a retiring member of the Executive Committee, I seek no further honors. The Central Association has already bestowed upon me its highest office. Therefore, I feel that I am, without bias, the proper person to introduce the following amendments to the Constitution, to be voted upon at our next annual meeting:

"Article I, regarding name, shall be changed to read: This society shall be known as the National Association of Obstetricians and Gynecologists.

"Article III, Section 1 (a) shall be changed to read: Physicians residing in the United States in good professional standing (the rest of the section to stand as it is).

"Article III, Section 1 (e) shall be changed to read: Membership shall be limited to 1,000 active members."

In 1950 President Randall's presidential address was devoted to the subject, but the society voted down the proposal to make the Central Association a national society. In 1950 the National Federation of Obstetric-Gynecologic Societies, which was made up of 45 obstetrical and gynecological

societies in the United States, was formed into the American Academy of Obstetrics and Gynecology, as a national organization. It was also hoped that it would take over the promotion of the gynecological pathology registry.

In 1951 the meeting was held in Detroit, with 461 official members, 100 life members, and 70 honorary members, present. At this meeting a calm settled over the membership, and again the spirit of freedom and friendliness prevailed. The pressure was off.

There have been national forces tending to raise the level of obstetrics and gynecology which were recognized by the Central Association, approved, and supported; at the same time sinister forces attempting to lower the standards were recognized and disapproved by the Central Association. The society has always led in progressive, conservative obstetrical and gynecological practice and development. Some have suggested that the Central Association membership be selected by invitation only. This has points for consideration, but it would then no longer be a democratic society.

There are two other special societies in this specialty—smaller and older, but with wider geographical scope—that are and always have been held in paramount respect and esteem and are spoken of with reverence. This fact should arouse our sense of responsibilty to develop leadership and improve the trained men in this society.

The Central Association has the heritage, background, and membership to enable it to continue to be the society in the Central States that will lead the way in achieving the highest standards in obstetrics and gynecology.

At this time let us take up and consider some of the excellent suggestions that were made by the Revisions Committee and submitted in 1951 by the Chairman, Dr. Hodgkinson of Detroit.

I wish to propose for your consideration a further study, and recommend adoption of the report of the 1951 Revisions Committee, which I will briefly summarize as follows:

Committee Report

1. Limitation of membership to 500.

2. No change in the geographic confines of the Association.

3. More specific definition of the professional criteria for membership: Seven years out of school with at least two years of gynecological training; limitation of practice to the specialty, qualified for Board certification; no other specialty acceptance; not judged by boards alone.

4. Continuance as a young men's group. Age limit of 60 years for "life members." Older members to be discussants of essays.

5. Transference of active members (by written request) to life membership after 10 years of interest and attendance.

6. No associate memberships; no university class controversies; *rigid selection for membership on the basis of the qualifications of the person alone,* as outlined by Membership Committee.

7. Careful check on attendance and dues and strict compliance with the Constitution and By-laws.

8. Rotation of members' participation in committees and offices as qualified.

9. Continued leadership in obstetrics and gynecology in the Central States. Loyalty to the society on the part of members. Acceptance only of men who are qualified for the high standards of membership in the Central Association.

PELVIC PAIN BASED ON A VASCULAR AND AUTONOMIC NERVOUS SYSTEM DISORDER*

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AS A CAUSE of gynecologic pain, the concept of a vascular disorder in the pelvis, suggested for the first time at least a century ago, has recently gained in favor. Its increased popularity is no doubt in part due to the modern physician's wide acceptance of the idea of a relationship between emotional states and functional or organic disease.

The argument in favor of this concept is disarmingly simple for the gynecologist. Effects of stress are typically manifested on autonomically innervated structures, especially on smooth muscle and, above all perhaps, on the smooth muscle of blood vessel walls. Pelvic physiology, except perhaps for that of the ovary, is to a large extent a smooth muscle physiology and particularly a physiology of blood vessels. Hence, it is to be expected that the effect of emotional stress in the pelvis should manifest itself as a vascular disturbance.[25]

Five years ago I reported a series of cases that seemed to belong to a more or less well-defined clinical entity and which it was thought could best be explained as the result of a pelvic vascular disturbance. The literature on this entity, which proved to be unexpectedly large, was likewise reviewed. As a result, the terms, "pelvic congestion," already widely used in the French literature, and "the congestion-fibrosis syndrome" were proposed. The latter designation, implying permanent organic change, has been difficult to justify and the simpler one has come into more general use.

The concept of "pelvic congestion" was offered at that time not as a proved condition but as the best available explanation of the signs and symptoms of a commonly observed clinical syndrome. As such it has been the subject of a little controversy. By some it has been seized upon uncritically as the final solution of a difficult gynecological problem. By others its existence, since incompletely proved, is entirely denied. The truth, that it is a useful working hypothesis, lies somewhere between these two views.

Since five years have elapsed since the original contribution it now seems proper to review the subject in the light of a number of new reports and of some new experience. Such a re-evaluation requires that three aspects of the problem be considered:

*Presented, by invitation, at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

I. First, the symptom complex must be analyzed again to determine whether even the clinical syndrome itself represents a consistent entity. This will be done on the basis of a series of 100 cases, all observed since the earlier collection was completed.

II. The essential nature of the disorder requires discussion and the value of the proposed explanation, that of pelvic congestion, must be compared with that of alternative theories.

III. Finally, the difficult and unsatisfactory problem of therapy must be more briefly referred to.

I. Clinical Aspects of the Syndrome

In the earlier paper[25] the symptomatology and physical signs of 105 cases were analyzed. The present study is based on a new series of 100 cases observed up to Jan. 1, 1953. These cases were not consecutive ones but were selected on the basis of their severity, so that the various manifestations of the disorder could be noted without the confusion resulting from the inclusion of many mild or doubtful cases. The report on these cases should be regarded therefore as description and not as a statistical survey of the problem as a whole.

The purpose of this article does not, however, end with the simple presentation of a clinical picture. It is also to establish certain facts about the syndrome which must be explained by any theory of causation which may be, permanently or provisionally, adopted.

Age Incidence.—

The patients of the 1948 series fell almost entirely within the twenty-year age period of the twenties and thirties (Table I). The majority of the patients in the 1953 series were also for the most part of these ages, although the recent cases have shown a greater spread, particularly into the decade of the forties.

This, then, is a disorder of the early and middle periods of ovarian function. It occurs in the years of greatest reproductive and sexual activity and is not predominantly a disorder of adolescence or the climacteric when most of the accepted endocrine disorders chiefly manifest themselves.

No instance of this condition occurring after the menopause is being reported in this series. Nevertheless, there are occasional instances observed of older women, with vague but troublesome low abdominal and back pain, and with tender uterosacral ligaments. The significances of such cases will be referred to later.

TABLE I. AGE INCIDENCE OF PATIENTS WITH THE PELVIC AUTONOMIC SYNDROME

YEARS OF AGE	15-19	20-29	30-39	40-49	50-	TOTAL
Series of 1948	1	56	39	8	1	105
Series of 1953	3	27	45	23	2	100

Marital Status.—

In the present series there were 87 married, 11 single, and 2 divorced women. This distribution was in general similar to that found in the group reported earlier.

There was a slight concentration of cases during the first years of marriage (Table II). These figures indicating a relationship of onset to time of marriage are certainly not conclusive, but do seem consistent with some general clinical impressions and with the report of Duncan and Taylor,[6] indicating an apparent relationship of the condition to marriage and parturition.

TABLE II. MARITAL AND REPRODUCTIVE STATUS OF PATIENTS

	TOTAL CASES	CHILDREN ONLY	CHILDREN AND ABORTIONS	ABORTIONS ONLY	NO PREGNANCIES
Unmarried patients	11			1	10
Married 1 year or less	8			2	6
Married 1 to 5 years	22	11	1	1	9
Married 5 to 10 years	19	7	6	3	3
Married over 10 years	38	18	13	3	4
Widowed or separated	2		1		1
Total	100	36	21	10	33

The disorder was certainly often first brought to the physician's attention many years after marriage. In such older patients, however, the symptoms were often found to be simply an exacerbation of a condition which, in variable intensity, seemed to have been existent for many years.

Reproductive Status.—

Evidence was submitted from the 1948 series that there was a relatively high incidence of infertility and an abnormal frequency of abortions, particularly of those artificially induced. These trends are again suggested in the 1953 series although less strikingly.

TABLE III. SUMMARY OF REPRODUCTIVE HISTORY

	CHILDREN ONLY	CHILDREN AND ABORTIONS	ABORTIONS ONLY	NO PREGNANCIES	TOTAL
Series of 1948	28	19	17	41	105
Series of 1953	36	21	10	33	100

Among even the 89 women who had been married, only 57 had had children (Table III). Forty-five per cent of the pregnancies in the 1948 series and 38 per cent in the 1953 series ended in abortion (Table IV). In each group, the relative incidence of induced abortion is also high.

TABLE IV. RESULTS OF ALL PREGNANCIES

	TOTAL PREGNANCIES	TERM PREGNANCIES	SPONTANEOUS ABORTIONS	INDUCED ABORTIONS
Series of 1948	145	80	37	28
Series of 1953	148	108	23	17

These figures tend to raise questions rather than to answer them. Do the factors causing the functional disturbance underlying pelvic congestion also predispose to spontaneous abortion? Are the induced abortions the causes of

a subsequent pathologic process in the pelvis or are they simply evidence of an unsatisfactory social environment that might be productive of psychologically induced symptoms?

General Symptomatology.—

An analysis of symptoms recorded in case histories may concern itself with the chief complaint only, in which case the record will be incomplete, or it may tabulate all complaints exhaustively and indiscriminately, in which case emphasis will be lost. In order to convey a true picture of the "congestion syndrome" an attempt has been made to give value to the different symptoms by recognizing three degrees of importance, namely, the chief complaint which brought the patient, additional complaints volunteered by the patient, and finally symptoms elicited by the physician through direct interrogation. This plan gives an opportunity to place the different symptoms in their approximate order of importance.

The chief complaints only are recorded from the 1948 and 1953 series in Table V. There is complete consistency between the series to the extent that low abdominal pain is the principal cause of the patient's visit to the physician.

TABLE V. PRINCIPAL SYMPTOMS IN EACH CASE

	SERIES OF 1948	SERIES OF 1953
Lower abdominal pain	59	60
Secondary dysmenorrhea	11	9
Low back pain	6	8
Menorrhagia	9	3
Sterility	7	3
Breast pain	4	3
Leukorrhea	3	1
Premenstrual tension	2	1
Dysuria	1	3
Intermenstrual bleeding	0	3
Dyspareunia	1	1
Others	2	5
Total	105	100

TABLE VI. SYMPTOMATOLOGY OF THE PELVIC AUTONOMIC SYNDROME

	PRINCIPAL COMPLAINT	SIGNIFICANT COMPLAINTS	ELICITED SYMPTOMS
Lower abdominal pain	60	73	81
Secondary dysmenorrhea	9	21	55
Backache	8	36	67
Dysuria	3	21	30
Breast pain	3	17	40
Sterility	3	9	13
Menorrhagia	3	10	18
Intermenstrual bleeding	3	15	29
Dyspareunia	1	7	47
Leukorrhea	1	28	50
Decreasing menstrual flow	1	4	29
Rectal pressure	1	18	
Repeated miscarriage	1	1	
Pruritus	1	4	
Vulval discomfort	1	2	
Premenstrual tension	1	4	
Abdominal distention		7	
Pain on sitting		2	
Premenstrual weight gain		2	
Pain in vagina		3	

After that in each group come secondary dysmenorrhea and low back pain. Beyond this point the list involves less common complaints and the frequency varies.

The complete symptomatology of the 1953 series is shown in Table VI, the severity of each symptom being measured by the priority which the patient seemed to attach to it.

A. Lower abdominal pain is the first in all categories. It is characteristically suprapubic in position, usually more marked on one side than the other, constantly present but variable in severity, made worse by fatigue, standing, sexual intercourse, and nervous strain.

B. Secondary dysmenorrhea is present in over half of the cases, but is less frequently offered by the patient as a major complaint. This dysmenorrhea appears characteristically some days before the onset of the menses and is diffuse and constant. It may be continued into the cramplike pain of the period itself or may even be completely relieved by the onset of menstruation.

C. Low back pain, often worse in the premenstruum and after standing, is a frequent accompaniment of the abdominal pain, but is rarely the primary complaint.

D. Dysuria is a common but minor symptom. The urine usually shows no pus and cystoscopy, if carried out, will reveal usually only a so-called "trigonitis" or localized hyperemia.

E. Premenstrual breast pain frequently begins at the same time as the pelvic symptoms.

F. Sterility is rarely a chief complaint. The histories show, however, that a considerable number of married patients, though not using contraceptives, had not conceived in many years.

G. Changes in the amount of the menstrual flow, i.e., a decrease or an increase, were noted by 47 patients. This point will be separately considered under the heading of changes in the menstrual cycle.

H. Intermenstrual bleeding, either spotting in the interval or pre- or postmenstrual staining, was fairly commonly reported by this group of patients, as it was in the 1948 series. It is not of great significance to the patient, since it appeared as a symptom usually only after a direct question was asked.

I. Dyspareunia is rarely a primary complaint, but is one of the most frequent symptoms reported when the patient is asked directly about it. The pain is perceived as deep in the pelvis and has probably the same cause as the parametrial tenderness which is such a prominent feature of the pelvic examination.

J. A mucous discharge from the cervix is almost invariably evident to the examiner. About half of all the patients are subjectively aware of what they regard as an abnormal amount of vaginal discharge.

K. A number of miscellaneous complaints, many characterized by some disturbance in sensation, are also occasionally reported. These include a sense of pressure in the rectum, puritus, vulval and vaginal pain, and discomfort when sitting or standing.

Types of Pain.—

Although other symptoms are present, pain of some type is the principal problem. The forms that this pain may take are shown in Table VII. Intermenstrual lower abdominal pain with tenderness is the most common. It is usually bilateral, but for some unexplained reason when it occurs on one side the right is the more frequent. The area of greatest tenderness is well below McBurney's point. The backache, dysmenorrhea, and dyspareunia have already been noted.

Rarely, the pain is acute in onset. Patients who develop such sudden attacks may be hospitalized and permanently stamped with a diagnosis of salpingitis or operated upon for acute appendicitis or ruptured ovarian cyst.

The exact source of the pain is not easy to explain. A hypersensitivity of the tissues may be a factor, but the distention of the parametria, uterus, and ovaries with increased intravascular or extravascular fluid seems also to contribute to the symptoms. The localization of the tenderness usually appears to the examiner to be in the parametria but it may at times be in the ovary.

TABLE VII. TYPES OF PAIN IN PATIENTS

	SUPRA-PUBIC BI-LATERAL	SUPRA-PUBIC RIGHT	SUPRA-PUBIC LEFT	BACK-ACHE	INCREASING DYS-MENOR-RHEA	DYS-PAREUNIA	ACUTE ATTACKS
Series of 1948	50	35	8	57	62	49	23
Series of 1953	47	25	11	67	55	47	9

Changes in the Characteristics of Menstruation.—

The changes in menstruation observed in this disorder are not striking except for the increase in dysmenorrhea already referred to (Table VIII):

A. The menstrual cycle (Table IX). In some patients there is a tendency for the periods to occur at three-week intervals and in others at about five weeks. This was evident in both the 1948 and 1953 series, but these alterations were not consistent and rarely took the form of either very frequent periods or of amenorrhea.

TABLE VIII. CHANGES IN MENSTRUAL PAIN

	NO CHANGE	PAIN DECREASING	PAIN APPEARING FOR FIRST TIME	PAIN INCREASING	ONSET OF AMENORRHEA
Series of 1948	37	6	27	35	0
Series of 1953	34	8	31	24	3

TABLE IX. CHANGES IN MENSTRUAL CYCLE

	NO CHANGE IN CYCLE	CYCLE BECOMING LONGER	CYCLE BECOMING SHORTER	CYCLE BECOMING IRREGULAR	ONSET OF AMENORRHEA
Series of 1948	80	9	13	3	0
Series of 1953	59	13	22	3	3

B. Changes in the duration of the menstrual flow (Table X) seemed more consistent. In a definite group, especially among the younger patients, there appeared a rather characteristic shortening and lessening of the flow. In other cases, there was an increase in the duration. This second type of change was more common in the older women of the series, in whom myometrial hypertrophy or the endocrine changes of the approaching menopause may have been complicating factors.

TABLE X. CHANGES IN DURATION OF MENSTRUAL FLOW

	NO CHANGE IN DURATION	DURATION SHORTER	DURATION LONGER	ONSET OF AMENORRHEA
Series of 1948	67	21	17	0
Series of 1953	50	29	18	3

C. Changes in the amount of the menstrual flow (Table XI), as reported by these patients, paralleled in general the changes in duration.

TABLE XI. CHANGES IN AMOUNT OF FLOW

	NO CHANGE IN AMOUNT	FLOW DECREASING	FLOW INCREASING	ONSET OF AMENORRHEA
Series of 1948	60	26	19	0
Series of 1953	46	31	20	3

D. Cyclical breast symptoms (Table XII). Slight premenstrual breast tenderness is so commonly an accompaniment of the menstrual cycle as to be considered normal. The earlier appearance of breast symptoms in the cycle, as well as their increase in intensity to the point of becoming a source of discomfort or anxiety, is evidence of at least a functional disorder. In both the present and the previous series breast symptoms often developed simultaneously with the pelvic disorder. This seems highly significant in indicating that the cause of this condition has a general or constitutional effect and is not limited locally to the pelvis.

TABLE XII. PREMENSTRUAL BREAST SYMPTOMS

	PAIN APPEARING WITH PELVIC SYMPTOMS	PAIN INCREASING WITH PELVIC SYMPTOMS	PAIN DECREASING WITH PELVIC SYMPTOMS
Series of 1948	41	8	1
Series of 1953	36	4	2

A review of the various characteristic alterations found in the menstrual cycles of these patients is of some aid in directing preliminary attention to the kind of agent that may be the cause of the syndrome. The timing of the menstrual cycle, the best single indicator of follicle-corpus luteum function, remains relatively unchanged. The alterations in amount and duration of flow, the occurrence of intermenstrual spotting and of pre- and postmenstrual staining, all suggest local vascular dysfunction. The pain and tenderness in

breast and pelvic organs seem to be explained only on the basis of an alteration in the threshold of pain sensitivity or perhaps of vascular change resulting in distention or stretching of organs or tissues.

Extragenital Psychosomatic Symptoms.—

It is characteristic for those suffering from psychosomatic disorders to have a multitude of symptoms, many referable to other organ systems than those that seem primarily concerned. In this respect the gynecologic psychosomatic disorder is no exception.

In Table XIII are shown the number of patients with what has been termed extragenital psychosomatic complaints. The frequency of these complaints is higher in the new series than in the old one probably simply because these complaints are now specifically inquired for in the taking of the history.

Beyond the figures for actual frequencies as shown in the Table, the observer gains certain impressions as to the specificity of these associated complaints. Some degree of *nervous tension* or emotional instability is complained of by fully two-thirds of the patients and *chronic fatigue* also seems of unexpected frequency and severity.

TABLE XIII. EXTRAGENITAL PSYCHOSOMATIC SYMPTOMS

	1948 SERIES	1953 SERIES
Nervous tension	35	65
Fatigue	29	25
Insomnia	17	32
Headaches	29	34
Gastric ("indigestion," "nausea," etc.)	24	43
Colonic ("spastic" or "mucous colitis")	15	26
Circulatory	15	14
Others	4	16

Among the complaints referable to other organ systems may be noted those of the colon. *"Spastic" and "mucous colitis,"* often severe enough to have sent the patient for x-ray studies, were frequently reported. This association seems also to have been noted by Goodall and Power[11] and by Willard Cooke.[3] Perhaps a similarity of autonomic innervation of colon and pelvic organs is an explanation of the apparently common association of a functional disorder in the two areas.

Psychiatric Status.—

The personality backgrounds and some of the underlying psychodynamic factors have recently been studied in detail in our Department, the results having been published in an article by Duncan and Taylor.[6] The findings in that study indicated that in general the women who developed pelvic congestion were immature individuals, often with histories of an insecure childhood and with a diminished, rather than an increased, sexual drive. The psychiatric status of the present group has not been systematically reviewed, but there were numerous reported instances of prior psychotherapy. Frigidity was noted in about half of the married women and appears highly characteristic of the disorder.

Previous Operations.—

As in the 1948 series, the histories of the present group showed a high incidence of previous operations (Table XIV). The commonest operation was that of removal of one ovary, or a part of one or both ovaries, for pelvic pain. These operations seem usually to have been carried out as an earlier and unsuccessful therapy of the condition for which the patient was again consulting a physician. Many of the 27 "simple appendectomies" also seem to have been performed under the mistaken assumption that the chronic lower abdominal pain from which the patient was suffering was due to a so-called chronic appendicitis.

The ovarian operations that had been performed in these cases point to one of the principal gynecologic problems today. When a so-called normal ovary reaches the pathology laboratory today it may often have been removed on account of the pain associated with pelvic congestion.

TABLE XIV. PATIENTS WITH PREVIOUS GYNECOLOGICAL OPERATIONS

	1948 SERIES	1953 SERIES
Operations on ovaries	11	15
Hysteropexy	7	2
Operations on tubes	2	1
Operations for myoma of the uterus	2	2
Dilatation and curettage	7	7
Vaginal plastics	2	0
Simple appendectomy	23	27
Total	54	54

Findings on Physical Examination.—

It is characteristic of pelvic congestion that the physical findings appear slight in relation to the severity of the subjective complaints (Table XV). The principal physical finding is tenderness, a physical sign to be sure, but one difficult to evaluate because of its dependence on the sensitivity of the patient. The subjective character of the syndrome contributes greatly to the problem of diagnosis in a given case as well as to the general characterization and recognition of the disorder as a clearly defined entity.

TABLE XV. OBSERVATIONS FROM PELVIC EXAMINATION

FUNDUS					OVARIES			CERVIX		PARAMETRIA	
RETROVERSION	LATEROVERSION	HYPERTROPHY	FIBROIDS	PREVIOUS OPERATIONS	ONE OR BOTH ENLARGED	ONE OR BOTH TENDER	PREVIOUS OPERATIONS	HYPERTROPHY	EROSION	TENDERNESS	"INDURATION"
25	6	31	3	5	28	55	15	16	34	93	2

A. The fundus uteri is usually in normal position in pelvic congestion. Although in the records of the present series the uterus was found in second- or third-degree retroversion in 25 and tipped to one side in 6, these figures may not differ much from a random sampling of the uterine positions of

normal women in these age groups. It seems probable, nevertheless, that a third-degree retroversion, especially if associated with some descensus, may contribute to the local vascular stasis and that rare cases may be benefited by the now much-condemned operation of round ligament suspension.

Hypertrophy of the uterus was though to be present in about one-third of the cases, the enlargement being due perhaps to a temporary congestion or a permanent proliferation of connective or muscle tissues. The enlarged uterus found in these cases is probably identical with what has been called "subinvolution."

B. The ovaries were regarded after palpation as being somewhat enlarged in 28 instances and as tender in 55 instances. These are the patients, often clinically described as having "cystic ovaries," who on exploration are found to have essentially normal organs or to have ovaries only slightly enlarged as a result of an accumulation of small cystic follicles. As noted before, 15 of the patients had already undergone operations on the ovaries.

C. The cervix nearly always shows some degree of hypersecretion. In 34 cases there was a well-developed erosion in the absence of any cervical laceration.

D. The parametria, especially the uterosacral ligaments, are the most consistent site of a definite physical sign. The tenderness at this point may be elicited by direct palpation of the ligaments through the posterior vaginal fornix or by lifting the cervix toward the symphysis by the examining fingers placed behind it. The tenderness in the uterosacral ligaments may be confirmed by rectal palpation, perhaps an important point in making the diagnosis.

II. The Theories of the Nature of the Underlying Disorder

The clinical syndrome which these tables have portrayed has been known for a long time. Recognizable descriptions of it date back well over a century and have appeared in many languages. It has, however, not emerged as a clear-cut entity, partly because of a confusing nomenclature, partly because of a constantly changing concept of the nature of the disorder underlying the symptoms.

TABLE XVI. TERMINOLOGY AND IMPLIED PATHOLOGY IN THE PELVIC AUTONOMIC SYNDROME

INFLAMMATION	MUSCULATURE	SENSORY NERVES	VASCULAR SYSTEM	GENERAL AUTONOMIC DISORDERS
Chronic parametritis	Spastische parametropathie	Grande névralgie pelvienne	Congestion pelvienne	Pelipathia vegetativa
		Plexalgie hypogastrique		Endosympathoses génitales
		Broad ligament neuritis	"Congestion-fibrosis" syndrome	Pelvic sympathetic syndrome

In Table XVI are shown some of the designations that have been used, arranged in groups according to the process which was believed to have been present:

A. The term under which this disorder has in the past been most widely known is that of "chronic parametritis," implying an inflammatory if not an infectious origin. This term was used by Schultze[24] in 1875 and by Freund[8] in 1885 in Germany, and is still widely employed by those with a middle European medical education.

B. A spastic condition of the smooth-muscle tissues of the pelvis was later proposed by Opitz,[22] and has received recent support from Martius.[19, 20] This theory was useful in explaining the apparent tenseness of the uterosacral ligaments.

C. That the condition was an affliction of the pelvic autonomic nervous system, primarily of the sensory components, has been the view particularly of the French school of gynecologists. On the basis of this assumed etiology we have had the euphonious terms, "plexalgie hypogastrique" and "grande névralgie pelvienne" (Cotte[4, 5]). An apparently similar concept has given rise in England to the more prosaic "broad ligament neuritis" (Young[29]).

D. Almost from the beginning of the clinical interest in the syndrome there have been those who were impressed with the vascular aspects. The idea of a pelvic congestion dates back to the writings of Gooch[10] in 1831 in England and by Recamier[23] in 1850 and Aran[1] in 1860 in France. A number of modern writers both in Germany (Kehrer[15, 16]) and France (Cotte[4]) and South America (Crottogini[12]) have continued to support this view and we have therefore the terms "congestion pelvienne" or "pelvic congestion."

E. Finally, as was to be expected, there arose a school which combined the three preceding views and regarded the condition as a general disorder of the pelvic autonomic nervous system, involving both sensory and motor pathways, and affecting all of the end organs of the system. On the basis of this concept the disorder has had a number of new terms applied to it. In France, it has become a group of conditions, collectively termed "endosympathoses génitales" (Netter[21]). In Germany it has been called "pelipathia vegetativa" (Gauss[9]; von Jaschke[14]) and "vegetative dystonie" (Klotz[17, 18]). Recently in England the simple designation "pelvic sympathetic syndrome" (Theobald[27]) has been used.

Before leaving this review of concepts one should refer briefly to a few other ideas of etiology that are currently held or have been held in the recent past. Goodall and Power[11] offered the idea of a pelvic allergy and used the term "metrallergy" for what appears from their description to have been the congested uterus. That a painful condition in the pelvis may be due to an ovarian deficiency has been proposed by Heckel.[13] Some support for this view may be found in the widely held belief in an estrogen cause for premenstrual tension, a disorder with some of the attributes of the condition under discussion. Finally, the view has been expressed that these pelvic complaints may be entirely psychiatric, hysterical manifestations, apparently without somatic components, imagined pains restricted to the mind of the patient (Cohen and associates[2]).

Discussion of Nomenclature and the Nature of the Disorder.—

The survey of these terms is not simply of historical interest and the question of nomenclature is not an idle one. The names adopted bring with them an acceptance of some special concept of the disease and from this therapy has to be developed.

As a result of the examination of clinical aspects, this syndrome appears most likely to be a disorder of the pelvic autonomic nervous system occurring in psychiatrically predisposed individuals as a result of stress of some kind. It manifests itself in a variety of ways, as disturbances in vascular function in the endometrium, perhaps in disturbances in myometrial contractility, certainly in a hypersecretion from the cervix, probably in shifts of extracellular fluid to produce swelling of certain organs, and apparently in a tendency to hyperalgesia in various areas supplied by the sensory components of visceral nerves. These are all disturbances in autonomic nervous system function and perhaps this disorder should be called *the pelvic autonomic syndrome.*

Yet there are probably other examples of gynecologic disorders dependent on the autonomic nervous system which cannot properly be included. One is the most frequent of all gynecological complaints, the common primary dysmenorrhea, which bears little resemblance to the condition under discussion. There are perhaps many others and some day there may be chapters in standard American textbooks entitled the "Disorders of the Pelvic Autonomic Nervous System." Yet, to create a "pelvic autonomic syndrome" seems to have about the same value as lumping together the disorders of the ovary as the "pelvic endocrine syndrome."

The possibility must also be considered, however, of recognizing two pelvic autonomic disorders, one concerned largely with vascular dysfunction ("pelvic congestion") and one with sensory change ("hypogastric plexalgia"). The equivalents of these two types can be rather easily differentiated as they occur in the breast. In some cases breast tenderness exists without any breast enlargement or signs of hyperemia and one then speaks of "mastalgia" or "mastodynia." In other cases the discomfort appears in association with premenstrual breast enlargement and vascular change is shown in the deepened color of the areolae. This one refers to a "premenstrual breast engorgement."

When the operator actually sees and palpates the typical swollen, soft, cyanotic uterus he can hardly avoid the acceptance of a vascular disorder. On the other hand, when pain in the region of the uterosacral ligaments persists after the menopause, the presence of a vascular factor is more difficult to accept.

Finally reference should be made to the term *congestion-fibrosis syndrome.* This has been used at times because it was believed that congestion of long standing might result eventually in connective-tissue proliferation, fibrosis, or hypertrophy. There is evidence that this process may be of frequent occurrence in the reproductive organs. Nevertheless, it remains a hypothesis

and the term should be employed in a tentative way, in the consideration of pathological relationships, rather than as a practical term in clinical diagnosis.

The best plan seems, therefore, to use the term *pelvic congestion* for at least the major portion of the cases of this group and to regard it as only one of perhaps several pelvic autonomic disorders. If this term is retained it must be regarded as provisional, pending a more complete study of the precise physiologic conditions that exist in the pelvic vascular system when this syndrome is clinically present. If this term is used, furthermore, it must be borne in mind that the vascular disorder is almost always associated with other signs of autonomic nervous system disturbance, such as changes in the secretory activity of certain glands, especially of the cervix, and a heightened responsiveness of the sensory nerves.

Evidence for a Vascular Factor.—

The evidence that a local circulatory condition is the dominant feature in the typical case of this syndrome needs to be briefly summarized.

In introduction there should be recalled the several factors or agents which may affect pelvic circulation. First, there are the obvious anatomical and mechanical factors. The intravenous pressure in the pelvis will vary with the patient's position. This change will be greater if the veins are poorly supported as the result of damage to the pelvic muscles or fascias at the time of a prior delivery. Second, there are the ovarian hormones, especially the estrogens, which cause a hyperemia and an increase in tissue fluids in their specific target organs. A third, but pathological factor, may be the presence of complicating inflammation which can be a cause of at least local hyperemia. Finally, there are the sympathetic and parasympathetic nerve supplies to the uterus and other pelvic structures which are capable of causing vasoconstriction and vasodilatation.

The theory being offered to explain the clinical syndrome that has been described is that the specific causes of pelvic congestion are "psychosomatic" or emotional factors made effective over the pelvic autonomic nerves. The state of the ovarian function, the intactness of the pelvic anatomical supports, and perhaps the complicating presence of infection, may, however, greatly vary the chance of development and the severity of the symptoms in a given patient.

Some of the points that indicate that this disorder depends largely on circulatory disturbances are the following:

A. The variations in severity of the patient's complaints can all be logically related to changes in circulation. The symptoms are at their worst during the premenstrual week when the abnormal congestion is superimposed upon the physiologic hyperemia. Improvement occurs, almost invariably, with the menopause when excessive vascularity in the genital organs becomes physiologically impossible. The condition is frequently worse after coitus, which from a physiologic standpoint is essentially a vascular phenomenon.

The patient is more uncomfortable after periods of standing and is relieved by the recumbent position, alterations to be expected if the condition depended to some extent on intravascular stasis.

B. The physical signs, in the typical, severe case, especially as seen at laparotomy, are themselves indicative of a vascular disorder. The uterus is softened, slightly enlarged, and purplish or mottled in color. The cul-de-sac contains an increased amount of amber-colored fluid and there is recognizable edema of the subserosal connective tissue and sometimes of the ovary.

C. Finally, it has been shown by Duncan and Taylor[6] that the pelvic vascular system is highly responsive to states of mind. With method dependent upon changes in thermal conductance, it was shown that variations in the pelvic blood flow took place whenever during a psychiatric interview subjects were touched upon toward which the patient had special emotional attitudes. This clinical experiment has not yet been carried to the point of showing that the pelvic vascular reactions of patients with congestion are excessive but only of demonstrating the presence of a mechanism that is highly consistent with the theory of pelvic vascular change as a psychosomatic disorder.

III. Therapy in Pelvic Congestion

If it is true that what we are dealing with in pelvic congestion is a psychosomatic syndrome we should not expect dramatic therapeutic results. In cases of "spastic colon," "nervous headaches," and "functional disorders of circulation," one attains improvement or remissions but only with the passage of time does a complete cure usually occur. This seems to be the case also with "pelvic congestion."

Results of Treatment in Present Series.—

The results in the treatment of the 100 cases in the present series are shown in Table XVII. It is to be noted that in 44 there was only a single visit or at most a very short period of observation. The remainder were observed over varying periods of time, the average being for 19 months.

TABLE XVII. RESULTS OF VARIOUS TYPES OF THERAPY

CONSULTATION ONLY	GENERAL NON-OPERATIVE THERAPY		MINOR SURGICAL PROCEDURE		CONSERVATIVE ABDOMINAL SURGERY		HYSTERECTOMY	
	UNIMPROVED	IMPROVED	UNIMPROVED	IMPROVED	UNIMPROVED	IMPROVED	UNIMPROVED	IMPROVED
44	17	11	6	5	2	8	0	7

The point should again be emphasized that these do not represent a typical sample of patients making their first appeal for medical aid on account of the congestion syndrome. The majority had had some previous therapy elsewhere and were referred as having special problems. Furthermore, of the cases seen, only those with definite and pronounced symptoms have been included in the series that has been analyzed. In such a series the

effect of treatment may appear more discouraging than is true for the average case. The frequency of surgical interference will also be many times higher than is to be anticipated in the unselected, previously untreated cases.

General nonoperative therapy includes consideration of rest, exercise, the common anxieties of life, and in some instances details of marital relationships. Over one-half of these cases were improved and perhaps this favorable figure should be greater since many of the 44 seen for a single visit only may have been so readily benefited by a simple explanation of the situation as to require no further treatment.

Minor surgical procedures mean essentially cautery of an infected or hypersecreting cervix. Treatment of the cervix was considered to be important by Young,[29] and recently Theobald,[27] writing of the "pelvic sympathetic syndrome," has reported a very high percentage of cures by means of a cauterization of the endocervical and endometrial cavities with silver nitrate. Admitting that the techniques used here were somewhat different, we cannot report any impressive percentage of cures by cautery of the cervix.

Conservative abdominal surgery was carried out in 10 cases (Table XVIII). The operations consisted of a round ligament suspension in 1 case; a resection of the presacral nerve in 2 cases; a presacral resection and bilateral oophorectomy in 1 case; a presacral resection and left salpingo-oophorectomy in 1 case; and various operations on the ovaries in 5 cases.

These are a perhaps somewhat miscellaneous group and it may be objected that the cases do not necessarily fall under the heading of the "congestion syndrome." The patients had in common the characteristic abdominal pains and the typical posterior pelvic tenderness. Some additional indication for surgery was, however, present in each case.

One patient, with a persistent sacral backache and a third-degree retroversion, was treated by a simple round ligament suspension. Four patients suffered from persistent dysmenorrhea, requiring monthly narcotics for relief. Of these, 2 (Cases 2 and 3) were treated by presacral resection and 2 others (Cases 4 and 5) by this operation combined with a partial removal of cystic ovarian tissue. The 5 remaining patients were all operated on for cystic enlargements of the ovary. Of these operations, 3 (Cases 6, 8, 10) were carried out because of a single or repeated attacks of acute pain and one (Case 9) for an infertility for which no other cause besides the cystic enlargement of the ovaries could be found. The last of this group (Case 7) was operated upon in another institution apparently also for an episode of acute pain.

Of the 10 cases, 8 seemed to have definite, although perhaps temporary, relief of symptoms. This is a more favorable experience than that noted in the 1948 series and is not consistent with the observation that, among the 100 patients in the present series, 15 had already had prior, and evidently unsuccessful, ovarian operations. It should be noted that these cases are reported simply as "improved" and not as "cured" for some symptoms usually persist as long as ovarian function continues.

TABLE XVIII. PATIENTS TREATED BY CONSERVATIVE SURGERY

CASE NO.	INITIALS	NAME OF OPERATION	AGE OF PATIENT	PREVIOUS CHILDREN	TIME MARRIED	DURATION OF SYMPTOMS	SPECIAL INDICATIONS	RESULTS
1	V. R.	Hysteropexy	35	1	Separated	1 year	Persistent pain	Improved at 3 months
2	R. G.	Superior hypogastric plexus resection	17	0	Single	3 years	Severity of symptoms	Unimproved at 11 months
3	A. H.	Superior hypogastric plexus resection	34	0	Single	14 years	Duration of symptoms*	Improved at 2 years
4	S. S.	Superior hypogastric plexus resection Bilateral partial oophorectomy	28	0	6 years	6 years	Severity of symptoms. Sterility	Unimproved at 9 months
5	K. D.	Superior hypogastric plexus resection Left salpingo-oophorectomy	32	2	10 years	18 months	Persistent pain	Improved at 4 years Pregnancy
6	R. M.	Left salpingo-oophorectomy	20	1	2 years	2 years	Torsion of cystic ovary	Improved at 2½ years
7	B. G.	"Salpingo-oophorectomy"	26	0	3½ years	3 years	Undetermined*	Improved at 2 years Pregnancy
8	R. L.	Right salpingo-oophorectomy	34	3	10 years	4 months	Severity of pain Possible appendicitis	Improved at 9 months
9	N. G.	Bilateral partial oophorectomy	22	0	3 years	3 years	Sterility	Improved at 12 months Pregnancy
10	C. W.	Bilateral partial oophorectomy	26	1	4 years	1 year	Severity of painful attacks	Improved at 21 months Pregnancy

*Operation performed in another institution.

Abdominal hysterectomy was performed in 7 cases (Table XIX). These operations were carried out in somewhat older women than those in the preceding group and only after a number of years of symptoms. In all but one of these there were indications in addition to the pain and tenderness.

In 3 patients (Cases 2, 3, and 5) menorrhagia was present and in 3 others (Cases 4, 6, and 7) previous conservative abdominal operations on the uterus or adnexa had failed to relieve symptoms. The remaining patient, 41 years of age with three children, had had symptoms of pelvic pain for 7 years.

The results of hysterectomy, so far at least as pelvic symptoms are concerned, appear to have been fairly good. The psychiatrist's fear that the neurotic patient after relief of pelvic pain will simply transfer her symptoms to some other organ remains a possibility, but it still seems probable that in certain rare and correctly selected patients hysterectomy will bring genuine improvement.

A Tentative Program of Therapy.—

The choice of therapy will depend on the age of the patient, her reproductive history, the duration and severity of symptoms, and the presence of complicating organic pathology.

The first step is the reassurance of the patient that the condition although troublesome is not serious or progressive. In the first or subsequent visits, factors of fatigue, situations of stress, and more specific problems of the marriage relationship may be considered. In the majority of the mild cases and those of short duration, improvement will result.

In rare cases some obvious organic trouble, such as a major degree of retroversion with descensus, requiring its own treatment, may be found. In many, cervicitis with erosion may be present and the treatment of this may have a beneficial effect.

If the symptoms have persisted for a year or more and the simple measures outlined have failed to produce results, an indefinite continuation of symptoms may be anticipated. In such situations the patient's plans for having children should perhaps be made the central guide to therapy. If there is sterility, treatment for this should be undertaken. If there is not, the patient should have explained to her the wisdom of having the children she plans at an early age. Pregnancy in some cases seems temporarily to alleviate symptoms, while delay may lead to infertility or eventuate in an operation.

At some point in the treatment of a severe case formal psychiatric assistance may have to be considered. The results of psychotherapy seem about as difficult to evaluate as those of surgery. Nevertheless, it has become for the last year the routine of this Department to have a psychiatric consultation before undertaking major surgery in cases of this type.

There will remain a few cases in which surgery may finally be resorted to. The cases for ovarian operations will be those with definite enlargements, which raise the possibility of neoplasm; those associated with acute attacks

TABLE XIX. PATIENTS TREATED BY HYSTERECTOMY

CASE NO.	INITIALS	NAME OF OPERATION	AGE OF PATIENT	PREVIOUS CHILDREN	TIME MARRIED	DURATION OF SYMPTOMS	SPECIAL INDICATIONS	RESULTS
1	S. L.	Complete hysterectomy	41	3	20 years	7 years	Persistent pain and premenstrual tension	Improved at one month
2	M. C.	Complete hysterectomy	39	4	20 years	"Years"	Menorrhagia	Improved at 21 months
3	E. F.	Complete hysterectomy Right salpingo-oophorectomy	38	2	9 years	"Years"	Menorrhagia	Improved at 1 month
4	S. B.	Complete hysterectomy Right salpingo-oophorectomy	37	3	13 years	7 years	Failure of previous conservative operation	Improved at 9 months
5	B. E.	Complete hysterectomy Bilateral salpingo-oophorectomy	42	1	22 years	5 years	Menorrhagia and dysmenorrhea	Improved at 24 months
6	E. B.	Complete hysterectomy Section of uterosacral ligaments	32	1	6 years	2½ years	Failure of previous conservative operation	Improved at 5 months
7	N. E.	Complete hysterectomy Section of uterosacral ligaments	42	1	22 years	5 years	Previous myomectomy Persistent dysmenorrhea	Improved at 4 months

of severe pain, in which differential diagnosis may be difficult; and perhaps a few cases of multicystic ovary to be operated upon in a final attempt to cure infertility.

Hysterectomy seems justified in a very small percentage of cases. These are the patients of 35 years and older, who have no wish for further children and who have had severe symptoms for a number of years. Operation in these cases becomes more justifiable if there is complicating menorrhagia or organic pathology in the pelvis. In the presence of pain alone psychiatric consultation is indicated before hysterectomy is undertaken.

Conclusions

1. A clinical condition with characteristic symptoms and physical signs frequently encountered in gynecological practice has been described. The principal complaints are various types of pain with secondary symptoms dependent on excessive secretion from the cervix, minor changes in the character of menstruation, and bladder irritability.

2. Many concepts have been held as to the nature of this disorder. The most likely explanation at present seems to be that it is chiefly a disturbance of vascular physiology. For this reason the term "pelvic congestion" seems for the present a proper designation.

3. Vascular change in the pelvic organs is produced physiologically by vasomotor impulses received over the pelvic sympathetic and parasympathetic systems. Pelvic congestion is then in a sense a "psychosomatic" disorder.

4. Other factors, however, also affect pelvic circulation, such as the steroid hormones, the anatomical supports of the uterus, and the position of the patient. Since these factors are also effective, pelvic congestion is not wholly "psychosomatic" in origin.

5. Therapy should be conservative with attention to the factors that may through nervous stress or emotional instability affect the pelvic autonomic nervous system. Logical treatment must also consider factors which affect the pelvic circulation locally, and should include care of the infected cervix and, if necessary, correction of pelvic floor relaxations or descensus.

6. In a few cases, when the pain is associated with enlarged ovaries, especially if the patient is sterile, conservative operations on the adnexa may be justified. In a few other cases in older women, if the disorder is of many years' standing and if other methods have failed, hysterectomy may be the therapy of choice.

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COMPARTMENTAL DISTRIBUTION AND SHIFT OF WATER AND ELECTROLYTES IN PRE-ECLAMPSIA*†

Part I. Distribution of Electrolytes in the Serum and Edema Fluid

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SODIUM retention in the toxemias as a manifestation of abnormal electrolyte metabolism has been demonstrated by Rupp,[1] Dieckmann,[2] and others. Clinically, sodium chloride limitation is of admitted value in the treatment of pre-eclampsia.

In order to treat pre-eclampsia effectively, the abnormalities of electrolyte and water metabolism must be better understood. The purpose of this investigation was to establish if possible some additional facts concerning the distribution of sodium, potassium, and chloride in the various body compartments of the patient with pre-eclampsia.

The first phase of this investigation was concerned with the concentrations of sodium, potassium, and chloride in the serum of both normal pregnant patients and patients having pre-eclampsia. The second phase of this investigation was concerned with the distribution of these same electrolytes between the serum and the edema fluid of both pregnant patients without pre-eclampsia and those having pre-eclampsia.

Experimental

All patients included in this study were within the last trimester of pregnancy. In most instances the serum and edema fluid were obtained from the patients prior to the institution of any therapeutic regime. A flame spectrophotometer‡ was used for all determinations of sodium and potassium. Chlorides were determined by the method of Schales and Schales.[3]

Routine determinations of sodium, potassium, and chloride were done on the serum of 44 patients with pre-eclampsia. A control series of 36 normal pregnant patients was similarly studied. The results obtained from these two series of patients are illustrated in Table I. The mean serum sodium concentration for the normal patients was 142.3 meq. per liter with a range of 136.7 to 146.9 meq. per liter; for the patients with pre-eclampsia, 137.5 meq. per liter with a spread of from 116.4 to 149.8 meq. per liter. Patients with pre-eclampsia were found to have serum sodium concentrations which averaged 4.8 meq. per liter less than that found in patients without pre-eclampsia. This difference is highly significant since the probability of its occurrence by chance is less than

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‡Process and Instruments Company of New York, N. Y.

1 in 1,000 similar comparisons.* There was no significant difference between the two groups with regard to the serum potassium concentrations. The mean serum potassium concentration in the nontoxemic patients was 4.14 meq. per liter with a range of from 3.6 to 5.1. For the patients with pre-eclampsia the serum potassium concentration averaged 4.2 meq. per liter with a range of from 2.5 to 5.4.

TABLE I. SERUM CONCENTRATIONS OF SODIUM, POTASSIUM, AND CHLORIDE

NORMAL PREGNANCY, 36 PATIENTS			PRE-ECLAMPSIA, 44 PATIENTS		
Na^+ MEQ./L.	K^+ MEQ./L.	Cl^- MEQ./L.	Na^+ MEQ./L.	K^+ MEQ./L.	Cl^- MEQ./L.
144.6	3.9	105.5	122.2	5.5	94.8
145.2	5.1	98.9	116.4	5.3	82.0
144.3	3.8	98.9	142.4	5.4	91.9
143.2	4.1	99.4	148.0	4.1	109.0
145.8	4.6	106.8	149.8	5.2	108.0
143.9	4.1	110.0	145.1	4.7	109.0
143.6	4.1	105.5	140.0	4.2	101.0
143.1	4.0	111.5	148.0	4.6	105.9
144.1	5.0	103.5	141.5	3.5	101.8
144.3	3.9	106.0	144.5	5.1	104.8
146.3	4.1	109.1	133.6	4.6	96.0
144.8	4.0	97.9	136.9	4.6	101.9
142.1	4.5	102.0	142.7	4.3	112.2
144.2	4.4	106.0	141.9	4.5	110.7
138.9	4.4	105.6	142.4	3.4	98.9
140.7	4.4	105.8	137.5	4.6	104.8
143.6	4.2	106.8	128.8	4.7	95.3
143.7	4.3	104.8	140.5	4.2	102.4
140.0	4.4	101.0	132.6	4.4	97.5
145.8	4.2	106.3	139.4	3.9	99.4
143.2	4.3	104.3	134.7	3.9	96.5
141.1	4.1	101.4	137.6	3.4	100.9
144.6	4.2	102.4	134.0	4.7	97.5
136.7	4.1	100.8	140.4	3.5	100.4
140.3	4.1	107.8	137.5	3.4	99.9
144.4	3.8	106.8	142.2	3.9	102.9
146.9	3.6	110.7	141.3	3.8	109.2
140.1	4.0	103.9	136.6	4.7	106.8
140.5	4.0	103.9	135.7	3.1	105.8
137.2	3.6	103.9	139.4	4.6	105.8
138.2	4.9	103.4	128.7	4.1	96.0
140.3	4.4	107.8	135.0	4.0	99.4
142.2	4.0	100.9	132.3	5.4	97.5
139.4	3.7	101.9	142.2	4.9	105.3
140.1	3.5	105.3	138.9	4.1	107.3
137.5	3.4	101.4	137.9	3.7	98.4
			137.1	4.0	104.3
			131.2	4.1	92.6
			134.0	3.9	99.9
			139.8	3.5	100.4
			133.8	3.5	95.5
			135.1	4.1	99.4
			139.5	2.5	94.0
			132.6	4.2	103.3
Mean 142.3	4.14	104.3	137.5	4.2	101.0

The mean serum chloride concentration in the nontoxemic patients was 104.3 meq. per liter with a range from 97.9 to 111.5; for the patients with pre-eclampsia, 101.0 meq. per liter with a range from 82.0 to 112.2. This difference is highly significant ($.005 > P > .001$).

*Probabilities were determined by Student's "t" test.

TABLE II. EDEMA FLUID CONCENTRATIONS OF SODIUM, POTASSIUM, AND CHLORIDE IN PREGNANT PATIENTS

SODIUM MEQ./L.			POTASSIUM MEQ./L.			CHLORIDE MEQ./L.		
SERUM	EDEMA FLUID	EDEMA FLUID MINUS SERUM	SERUM	EDEMA FLUID	EDEMA FLUID MINUS SERUM	SERUM	EDEMA FLUID	EDEMA FLUID MINUS SERUM
Without Pre-eclampsia.—								
140.5	133.2	−7.3	3.99			103.9		
141.1	141.9	0.8	4.74			102.4		
143.6	141.1	−2.5	3.76			99.9		
138.2	138.9	0.7	4.86	3.41	−1.45	103.4	110.2	6.8
140.5	142.2	1.7	4.05	3.73	−0.32	107.8	113.6	5.8
140.3	141.3	1.0	4.42	4.31	−0.11	107.8	110.3	2.5
139.4	139.7	0.3	3.71			101.9		
140.1	140.8	0.7	3.53	3.31	−0.22	105.3	112.7	7.4
Mean		−0.58			−0.53			5.6
With Pre-eclampsia.—								
139.1	142.5	3.4	4.32			107.8	119.0	11.2
141.9	145.0	3.1	4.49			110.7	121.4	10.7
140.5	143.2	2.7	4.20	3.40	−0.80	102.4	109.2	6.8
139.4	139.1	−0.3	4.64			105.8	114.1	8.3
134.0	136.2	2.2	4.73			97.5	107.8	10.3
136.1	138.4	2.3	3.44	3.72	0.28	97.9	107.5	9.6
132.6	133.2	0.6	4.23	3.71	−0.52	103.4	110.2	6.8
139.2	140.5	1.3	3.83	3.89	0.06	111.1	112.3	1.2
137.5	139.2	1.7	4.61	4.38	−0.28	104.8	106.8	2.0
133.6	140.4	6.8	4.55	4.09	−0.46	96.0	110.2	14.2
136.9	140.1	3.2	4.57	4.28	−0.29	101.9	104.3	2.4
142.7	145.9	3.2	4.33	3.68	−0.65	112.2		
140.5	143.3	2.8	3.48	2.93	−0.55	105.8	116.6	10.8
140.2	139.9	−0.3	5.18	3.73	−1.45	103.4	113.6	10.2
146.1	144.2	−1.9	3.80	3.64	−0.24	108.3	109.1	0.8
144.0	143.8	−0.2	3.50	3.28	−0.22	99.9	106.3	6.4
137.6	138.7	1.1	3.43			100.9	111.7	10.8
137.7	141.9	4.2	4.03	3.80	−0.23	102.9	113.2	10.3
138.5	138.5	0.0	3.36	3.05	−0.31	105.3	114.6	9.3
141.3	144.2	2.9	3.77	3.54	−0.23	109.2	118.1	8.9
136.6	139.7	3.1	4.65	3.81	−0.84	106.8	114.6	7.8
140.5	141.6	1.1						
135.7	141.1	5.4	3.14	3.48	0.34	105.8	114.6	8.8
141.7	140.9	−0.8	4.27	4.13	−0.14	102.9	112.2	9.3
137.1	142.2	5.1	4.00	3.77	−0.23	104.3	114.6	10.3
144.6	146.3	1.7	3.32	3.09	−0.23	103.8	112.1	8.3
149.5	150.8	1.3	3.45	3.92	0.47	109.5	118.6	9.1
130.7	130.2	−0.5	4.00	3.99	−0.01	101.9	109.2	7.3
141.8	144.7	2.9	4.40	4.12	−0.28	104.3	117.5	13.2
142.7	145.0	2.3	3.40	3.19	−0.21	110.3	118.2	7.9
139.5	142.7	3.2	4.20	3.89	−0.31	106.3	117.5	11.2
Mean		2.05			−0.29			8.4

The development of edema is a common clinical manifestation of pre-eclampsia. The etiology remains unknown. In an attempt to clarify some of the factors involved in the production of edema, the relationship between the concentrations of sodium, potassium, and chloride in the serum and in the edema fluid was determined. The edema fluid was collected by inserting a 14 gauge needle into the subcutaneous tissue in the pretibial area. A plastic catheter with multiple perforations was inserted through the needle. The needle was then removed leaving the catheter in place. An ample volume of edema fluid was consistently obtained within a 20 to 30 minute interval. The blood samples

for serum electrolyte determinations were drawn some time during the 20 or 30 minute interval required for the collection of edema fluid. Two groups were included in this investigation. The first group consisted of 8 patients who had demonstrable dependent edema and no evidence of pre-eclampsia. The second group consisted of 31 patients with demonstrable edema and pre-eclampsia. The results of the determinations are illustrated in Table II. The mean of the difference in concentration of sodium in the serum and edema fluid in the patients without pre-eclampsia was 0.58 meq. per liter, the serum having the higher concentration. On the other hand, in patients with pre-eclampsia the concentration of sodium in edema fluid was greater, the mean difference being 2.05 meq. per liter. The difference between the means of these two groups is highly significant ($.005 > P > .001$).

The concentration of potassium in the edema fluids of both groups was consistently less than that found in the corresponding sera. The difference between the two groups is not significant ($P = 0.30$).

The concentration of chloride in the edema fluids of both groups was consistently greater than that of the sera. The edema fluids of pre-eclamptic patients averaged 2.8 meq. per liter more chloride than found in the edema fluids of patients without pre-eclampsia. The is probably not a significant difference ($0.20 > P > 0.10$).

Comment

The observation, reported by Rossenbeck[4] and confirmed in this investigation, that there is frequently a lower serum sodium concentration in pre-eclampsia than in the pregnant patient without pre-eclampsia seems very logical. There have been repeated statements in the literature to the effect that although sodium retention in the toxemic patient is generally accepted as a fact, no evidence has been presented which indicates that the serum sodium concentrations in patients with pre-eclampsia are higher than those in normal pregnant individuals. It would seem more logical, if the tissues of patients with pre-eclampsia show abnormal degrees of sodium retention, that there should be a decrease rather than an increase in serum sodium concentration.

The data from this investigation furnish additional support for this logic inasmuch as they indicate that the edema fluid from patients with pre-eclampsia contains a higher concentration of sodium in comparison to the respective serum than is found in edema fluid from pregnant patients having no evidence of pre-eclampsia. This observation is interpreted as additional support for the supposition that in pre-eclampsia the sodium is withdrawn from the vascular compartment and tends to accumulate in the extravascular compartment. Chloride metabolism is altered in pre-eclampsia in a manner more or less parallel to that of sodium. Therefore these data do not support the findings of Rossenbeck[4] that there is a reciprocal relationship between serum sodium and chloride. There is, however, no justification for the assumption that both sodium and chloride are involved as unionized sodium chloride. De Alvarez and Gabrio[5] have previously stressed this point. This investigation has given no indication that potassium metablism is seriously affected by pre-eclampsia.

Summary and Conclusions

1. The serum sodium and chloride concentrations in patients with pre-eclampsia are lower than in normal pregnant patients.

2. A shift of sodium from the vascular into the extravascular space has been demonstrated by the fact that the concentration of sodium in the edema fluid from patients with pre-eclampsia is greater than in the serum.

3. There is no significant difference in the concentration of sodium in the edema fluid and serum of pregnant patients having edema but no pre-eclampsia.

4. Potassium and chloride concentrations in edema fluid were essentially the same in both normal pregnant and pre-eclamptic patients.

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PREGNANCY SUBSEQUENT TO LIGATION OF OVARIAN VESSELS AND THE INFERIOR VENA CAVA*

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THE course of six pregnancies subsequent to ligation of the inferior vena cava was reported from the Department of Obstetrics and Gynecology of Tulane University in 1949.[1] In September, 1952, Heath and Carpenter[2] and Burke and Rosenfield[3] reported two such cases. We are now bringing to date all cases observed in our Department.

In 1941, the procedure of bilateral ovarian vein and inferior vena cava ligation in suppurative pelvic thrombophlebitis[4] was initiated on the Tulane Gynecology Service as a lifesaving procedure. As of Sept. 1, 1953, 102 of these operations have been performed. The follow-up of 70 of these cases has been reported in detail.[5, 6, 7] It has been shown that there is little disturbance in pelvic physiology subsequent to the surgery. In addition, we emphasized that leg edema was minimal and that varices or disability did not result. The development of adequate collateral circulation was evident. Robinson[8] studied these channels and reported his findings in 1949. Burch and Ray[9, 10] have done extensive studies of venous and tissue pressures subsequent to ligation of the inferior vena cava and have shown there is no correlation of increased venous pressure and edema in these subjects. They further revealed that there is a trend of return from initial high venous pressure of the legs toward the normal after a six-month postoperative period.

DeCamp and co-workers[11, 12] observed persistent ambulatory venous hypertension in the legs of some patients studied postoperatively. Edema in these patients was minimal as were other clinical symptoms. These observations are reviewed to indicate that adequate circulatory compensation does occur following inferior vena cava ligation.

A review of these clinical observations has convinced us that this lifesaving procedure does not necessarily result in a handicapped individual. In addition, studies of ovulation as indicated by pregnancy, and endometrial biopsies revealed that the majority of these patients showed normal ovarian-uterine function; i.e., 29 of 35 patients (83 per cent) studied[7] showed evidence of ovulation as determined by pregnancy, secretory endometrium, or corpora lutea.

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The follow-up on our present series of 102 inferior vena cava and ovarian vein ligations reveals that 65 patients are within the childbearing age. Of the remainder, 21 are over the age of 50 years or had had hysterectomy or radiation at the time of or subsequent to the cava ligation. Twelve patients died in spite of the surgical attempts at cure and an additional 4 died within the past 12 years of unrelated causes. Of these 65 potential mothers with the cava ligated, 13 (20 per cent) have conceived a total of 18 times (Tables I and II).

TABLE I. INFERIOR VENA CAVA LIGATION

1941 through Aug. 31, 1953	102
*Operative failures	12
Total	90
†Deaths unrelated	4
Total	86
Had radiation, hysterectomy, or were over age 50	21
Total potential mothers	65

*Any death within 12 months of ligation.
†Deaths unrelated in any way to the disease or surgery.

TABLE II. NUMBER OF POSSIBLE PREGNANCIES

Potential mothers	65
Number patients that conceived	13
Percentage	20.0

Twelve of these women (who conceived after vena cava ligation) had had suppurative pelvic thrombophlebitis following abortion or delivery. The thirteenth case followed pelvic surgery. In most instances, at the time of the ligation, sections of one or both ovarian vessels were obtained for pathologic study. In one case, the right ovary, tube, ovarian vein and artery, and a segment of the vena cava were removed en bloc for a thrombus that extended into the vena cava. This case has been reported in detail elsewhere.[13] Another had multiple peritoneal abscesses, bilateral tubo-ovarian abscesses and such extensive pelvic and intestinal adhesions that ligation of the left ovarian vein had to be accomplished by retroperitoneal dissection from the right side. Both these patients have subsequently delivered live children. Table III shows the veins involved, sites of infarction, other pathology encountered, and associated surgery in these 13 cases. The outcome of the subsequent pregnancies is shown.

Five patients aborted spontaneously, one on two occasions. There was an additional criminal abortion. Thus 7 of the 18 pregnancies failed to reach viability (Table IV). This is admittedly a high figure but one must consider that the majority of these individuals had previously shown no desire for more children as indicated by the number of criminal abortions which initiated the original disease (Tables V and VI). In addition, the nature of the pathological changes in the uterus, tubes, and ovaries following severe pelvic sepsis undoubtedly reduced the possibility of optimal implantation and intra-

TABLE III. PREVIOUS OBSTETRICAL HISTORIES

NAME	CAUSE*	DATE OF LIGATION			VEINS INVOLVED	INFARCTION	ASSOCIATED PATHOLOGY	ADDITIONAL SURGERY	SUBSEQUENT PREGNANCIES
		MO.	DAY	YR.					
1. E. W.	Del.	9	2	42	R. and L. ov., R. uterine	None	None	None	Del. ×3
2. R. S.	Ab.	8	25	44	L. common iliac, L. ov., inferior vena cava	None	None	None	Del.
3. M. B.	Del.	10	30	44	L. ov.	Spleen, pul.	None	None	Ab. ×2
4. R. E.	P.O.	3	16	45	None grossly	None	None	None	Del.
5. M. S.	Ab. c	5	25	46	L. ov.	None	Pelvic absc.	None	Ab.
6. A. L.	Del.	5	23	47	R. ov.	Pulmonary	Fibroids	None	Ab.
7. L. P.	Ab. c	8	22	47	None grossly	None	None	None	Ab.
8. D. P.	Del.	8	30	47	L. hypogastric, L. ext. and common il., L. uterine	None	None	None	(Sect.) Del. ×2
9. M. M.p	Ab. c	9	15	47	R. ov., R. uterine	None	None	None	Del.
10. A. B.	Del.	12	17	48	R. femoral, R. iliac	Pulmonary	None	None	Del.
11. A. H.	Ab. c	9	10	49	R. ov. into cava	Pulmonary	None	R. salpingo-oophorectomy, resection 2 cm. inf. cava	Ab. Del.
12. A. D.	Ab. c	4	6	50	R. uterine, L. ov.	Brain (Absc.)	None	None	Ab. c
13. M. M.	Ab. c	7	7	50	Bilateral ov. and pelvic	None	Multiple perit. abscesses, R. and L. tubo-ovarian abscess	Aspiration of abscess and drainage	Del.

*Ab., abortion; c, criminal; Del., delivery; P.O., operation.

uterine growth. There was no apparent correlation between the time interval since ligation and the fate of the subsequent pregnancy (Table VII).

TABLE IV. RESULTS OF PREGNANCIES AFTER LIGATION OF THE VENA CAVA

13 Patients Who Conceived.—	
Total abortions	7
Total live births	11
Total pregnancies	18

TABLE V. PRELIGATION PREGNANCY AND SUBSEQUENT PREGNANCY

NAME	PRELIGATION	DATE OF LIGATION MONTH	DAY	YEAR	SUBSEQUENT PREGNANCY	SUBSEQUENT PREGNANCY	SUBSEQUENT PREGNANCY
1. E. W.	Delivery	9	2	42	Delivery Jan. 46	Delivery March 47	Delivery May 48
2. R. S.	Abortion	8	25	44	Delivery May 48		
3. M. B.	Delivery	10	30	44	Abortion, spont. Aug. 45	Abortion, spont. Jan. 50	
4. R. E.	Postopera-tive	3	16	45	Delivery April 47		
5. M. S.	Abortion, criminal	5-	25	46	Abortion, spont. Nov. 46		
6. A. L.	Delivery	5	23	47	Abortion, spont. June 49		
7. L. P.	Abortion, criminal	8	22	47	Abortion, spont. March 53		
8. D. P.	Delivery, section	8	30	47	Repeat section Nov. 48	Repeat section Nov. 50	
9. M. M.p	Abortion, criminal	9	15	47	Delivery June 50		
10. A. B.	Delivery	12	17	48	Delivery Jan. 50		
11. A. H.	Abortion, criminal	9	10	49	Abortion Nov. 50	Delivery Sept. 52	
12. A. D.	Abortion, criminal	4	6	50	Abortion, crim. Jan. 50		
13. M. M.	Abortion, criminal	7	7	50	Delivery April 52		

TABLE VI. INCIDENCE OF ABORTION AFTER LIGATION

Abortion prior to cava ligation	7 patients	
Subsequent abortions	4 patients	59.14%
Delivery or surgery prior to cava ligation	6 patients	
Subsequent abortions	2 patients	33.33%

The remaining 11 pregnancies produced viable children. These pregnancies occurred in 8 individuals, one of whom had a spontaneous abortion in the interim following her cava ligation. One patient has had two viable children by cesarean section for a contracted pelvis; another had had three spontaneous term births. The remainder have had one child each. One of the latter just recently had an abdominal hysterectomy for prolapse and

chronic cervicitis. At the time of surgery, 5 years subsequent to the cava ligation, a corpus luteum of the ovary was noted and the endometrium was secretory in type.

TABLE VII. INTERVAL BETWEEN LIGATION AND SUBSEQUENT PREGNANCIES

Years	Months 1	2	3	4	5	6	7	8	9	10	11	12
6		xx						000		x		
5						00	x					
4	00		00	0				0	0			
3	x 0											
2		x	0 0						0			
1						x		x (c)				

x, abortion, xx, second abortion.
c, criminal.
0, delivery, 00, second delivery, 000, third delivery.

The course of pregnancy in these patients was uncomplicated. The 7 instances of abortion revealed no undue blood loss or other complications. One of the 7 required surgical evacuation for completion, the remainder completed spontaneously (Table VIII).

TABLE VIII. ABORTIONS
SIX PATIENTS—SEVEN ABORTIONS

NAME	DATE	WEEKS PREGNANT	COMPLICATIONS
M. B.	8/31/45	8	None
	1/25/50	16	None
A. D.	1/ 6/50	8	Criminal, none
A. L.	6/ 2/49	16	None
L. P.	3/29/53	16	None
A. H.	11/ 9/50	8	None
M. S.	11/ 5/46	6	Curettage

In the 11 pregnancies that proceeded to viability, 4 terminated at 36, 37, 38, and 38 weeks, respectively, the latter 2 being repeat sections. All produced live babies (Table IX).

The course of these pregnancies as shown (Table IX) was uncomplicated by leg varices, congestion, excess bleeding, or complications of delivery or the puerperium. The examination at six weeks post partum revealed normal involution of pelvic structures in all 18 instances.

Comments

Since venous ligation as a method of control in thromboembolic disease is an accepted treatment, we can expect that the procedure of inferior vena cava ligation may be done on women who are still in the childbearing years.

TABLE IX. VIABLE BIRTHS

NAME	DATE	WEEKS' GESTATION	METHOD OF DELIVERY	EDEMA	VARICES			LACERATIONS	PLACENTA	BLOOD LOSS	POST-PARTAL COMPLICATION
					LEG	VULVA	HEM.				
A. B.	3/21/50	37	Spont.	2+	√						0
A. H.*	9/19/52	36	Spont.						Manual removal		0
M. M.	4/ 2/52	40	Spont.	1+	√			√			0
M. M.p	5/10/51	40	Spont., forceps							> 300 c.c.	0
R. S.	5/48	40	Spont., forceps and episiotomy								0
R. E.	4/47	40	Spont., forceps and episiotomy								0
E. W.	1/46	40	Spont.								0
	3/47	40	Spont.								0
	6/48	40	Spont.								0
D. P.	11/48	38	Repeat section								0
	11/50	38	Repeat section								0

*Threatened to abort.

It is known that subsequent disability of any degree occurs only infrequently. We have in addition shown that pelvic physiology following the ligation of the normal venous return of the pelvic organs is not necessarily hampered. We believe that, when manifest, the alterations of function are due to the primary pathologic entity rather than to the surgical procedure of cava ligation. These 18 pregnancies and the 11 live children resulting are proof that women who have had these vessels ligated may be reassured as to the possibility of conception and of safety during pregnancy and delivery. The possibility of abortion appears to be greater in these women but other complications apparently do not occur. A history of inferior vena cava ligation is not an indication for therapeutic abortion.

Conclusion

Pregnancy subsequent to ligation of the inferior vena cava and ovarian vessels may be expected to pursue a normal course without the development of other complications other than those experienced in pregnancy by the woman who has not had ligation of these vessels.

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Discussion

DR. WM. J. DIECKMANN, Chicago, Ill.—Medicine owes much to Collins and his group who, despite criticism, have developed a safe technique for the prevention of pulmonary emboli by the ligation of the inferior vena cava. The procedure is even being used in certain cases of cardiac failure. Unquestionably, they have ligated the vena cava in a few patients who might have recovered without operation, but they and others have shown that the operation itself carries very little mortality even in the seriously sick patients and does not result in any chronic disorder of the lower extremities.

Prior to 1926 and up to 1929, we averaged one maternal death per year from multiple lung infarcts and abscesses caused by puerperal pelvic thrombophlebitis. Schwarz and I, in 1926, discussed the ligation of both ovarian and the internal iliac veins in certain cases of pelvic thrombophlebitis. The mortality from pelvic thrombophlebitis due to anaerobic streptococci was 78 per cent, but, in 1910, the above ligation, as reported by Schottmüller, lowered the mortality to 30 per cent. Because we adovcated uterine culture, removal of placental tissue from the uterus, and suggested the vein ligation in selected cases, there

was some discussion by the society as to the advisability of publishing such a report. Today, almost everyone practices early uterine culture and the removal of placental tissue from the uterus with insistence on proper uterine drainage. The words "radical" versus "conservative" always enter such discussions. Conservatism, resulting in death, is extremely radical.

Despite the use of aseptic surgery, sulfonamides, and antibiotics, pelvic thrombophlebitis still occurs in both obstetric and gynecologic patients and will cause death.

You may never have had a patient in whom this operation was indicated or, which is more probable, you had such a case, did not recognize the seriousness until too late, and the patient died. Extensive studies have been made in the authors' Hospital of the immediate and late effects of ligation of the vena cava. All the results indicate that there are no alarming sequelae and that only good results follow if the operation is performed early enough. The technique for exposure is simple and I have used it in a number of cases for obtaining biopsies from the kidney. They have reported normal menstruation occurring after the operation and now they report that, of the women in the reproductive period, 20 per cent conceived; unquestionably others could have conceived had they so desired.

The obstetrician, in particular, must have "fire drill." Frequently the emergency requires immediate treatment, be it postpartum hemorrhage, an ectopic pregnancy, eclampsia, or pelvic thrombophlebitis. I urge all of you, at the end of a simple hysterectomy, to expose the inferior vena cava in a few cases to familiarize yourselves with the technique and the relative ease of the operation.

DR. COLLINS (Closing).—I would like to thank you, Dr. Dieckmann, for your discussion—in support, I take it. I remember that during one of these operations (not one of them in this series), Dr. Dieckmann was standing right at my side. Fortunately we found a little clot, so we were able to convince him that maybe it was necessary, at least in that case.

OVARIAN TUMORS COMPLICATING PREGNANCY*

A Review of 45 Surgically Proved Cases

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OVARIAN tumors complicating pregnancy present challenging diagnostic and therapeutic problems. Two recent experiences stimulated our interest in this subject. The first was a group of three patients presenting typical clinical pictures of ectopic pregnancy who, at laparotomy, were found to have normal intrauterine pregnancies complicated by ovarian tumors. The second experience was the diagnostic and therapeutic problem presented by a patient with a 2½ months' pregnancy complicated by a 35 cm. serous cystadenoma of the ovary.

The literature on ovarian tumors complicating pregnancy has been brought up to date in a comprehensive article in 1949 by Hamilton and Higgins.[1] They also reported 21 cases of their own. Haas[2] in 1949 reported 25 additional cases. Dougherty and Lund,[3] in 1950, reviewed the management of solid ovarian tumors in pregnancy, collected 30 cases from the literature, and reported 6 of their own.

Since any personal series would be too small to permit any significant conclusions, we reviewed the obstetrical records of four Indianapolis hospitals† covering the past ten years and representing well over 100,000 pregnancies. We have collected and analyzed 45 cases of surgically proved ovarian tumors, 6 cm. or larger, complicating pregnancy. These cases represent the experiences of 20 different physicians. We have included only those ovarian tumors confirmed by surgery because the others were of borderline size, remained asymptomatic, and the type of tumor could not be determined.

Incidence

The incidence of ovarian tumors, 6 cm. or larger, complicating pregnancy varied in the different hospitals from 1:1,000 to 1:8,000. The true incidence was probably higher as tumors which remain asymptomatic may escape diagnosis until the late puerperium. In this series, even a 16 cm. pseudomucinous cystadenoma escaped detection until 10 days post partum when it suddenly twisted on its pedicle 5 days after the patient had left the hospital.

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†Indiana University Medical Center, Indianapolis General Hospital, Methodist Hospital, St. Vincent's Hospital. We are indebted to the staff physicians of these hospitals who have so generously permitted us to report their cases.

Types of Ovarian Tumors

Table I shows the variety and size of ovarian tumors encountered in this series. The incidence of the tumors showed no relationship to the age and parity of the patients.

TABLE I. OVARIAN TUMORS COMPLICATING PREGNANCY, 45 CASES

TYPE OF TUMOR	NO. OF CASES	SIZE OF TUMOR (CM.)	TIME OF DIAGNOSIS					
			FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER	CESAREAN SECTION	DURING LABOR	POST PARTUM
Dermoids (1 bilateral)	18	6-18	11	3		1	3	
Serous cystadenomas	11	8-35	7	3	1			
Corpus luteum cysts	4	6-8	2			2		
Pseudomucinous cystadenomas	3	15-20			1		1	1
Endometrial cysts (1 bilateral)	2	8-9	1		1			
Parovarian cysts	2	6-7			1			1
Fibroma	1	10		1				
Adenocarcinoma	1	10		1				
Krukenberg (bilateral)	1	19 and 17		1				
Luteal cyst (bilateral)	1	12 and 12	1					
Edema of ovary	1	9		1				

Diagnosis

Careful bimanual pelvic examination in the first trimester of pregnancy will usually identify the existence of an ovarian tumor. However, the interpretation of the pelvic findings of an adnexal mass may present considerable diagnostic and therapeutic difficulty. As evidenced by our data, 36 per cent were misdiagnosed (Table II).

TABLE II. INCIDENCE OF INCORRECT DIAGNOSIS

	TOTAL CASES*	INCORRECT DIAGNOSIS	
		NO. CASES	PERCENTAGE
First trimester	22	6	28
Second trimester	10	2	20
Third trimester	4	4	100
Labor	4	2	50
Post partum	2	1	50
Total	42	15	36

*In 3 additional cases, tumor found incidentally at section.

In this series of 45 cases, the diagnosis of the existence of an ovarian tumor was established during the first trimester in 22 cases, during the second trimester in 10 cases, at term in 4 cases, during labor in 4 cases, and in the early puerperium in 2 cases. In 3 additional cases, asymptomatic ovarian tumors were found incidentally at cesarean section.

A. First Trimester.—

The interpretation of an adnexal mass in the first trimester presents a real problem. Our data show that 6 of the 22 cases were incorrectly diagnosed (as shown in Table III). It may be impossible to differentiate ectopic pregnancy from smaller ovarian tumors, especially a bleeding corpus luteum cyst with intraperitoneal hemorrhage. In 5 of our 6 cases, laparotomy had been performed with a preoperative diagnosis of ectopic pregnancy. In the other case, a serous cystadenoma adherent to the uterus had been incorrectly interpreted as a uterine fibroid. In our experience, we have also diagnosed several adnexal masses in early pregnancy as ovarian tumors which later proved to be uterine fibroids.

TABLE III. INCORRECT DIAGNOSES

PREOPERATIVE DIAGNOSIS	GESTATION	SURGICAL FINDINGS	
First Trimester.—			
1. Ectopic	3 weeks	Endometrial cyst	8 cm.
2. Ectopic	6 weeks	Corpus luteum cyst	6 cm.
3. Ectopic	6 weeks	Corpus luteum cyst	6 cm.
4. Ectopic	8 weeks	Twisted dermoid	6 cm.
5. Ectopic	8 weeks	Dermoid	8 cm.
6. Uterine fibroid	8 weeks	Serous cyst	8 cm.
Second Trimester.—			
1. Appendicitis	20 weeks	Twisted serous cyst	9 cm.
2. Abdominal pregnancy	20 weeks	Edema of ovary	9 cm.

B. Second Trimester.—

The presence of an ovarian tumor was diagnosed in the second trimester in 10 cases. In most cases the ovarian tumor could be palpated distinctly separate from the enlarging uterus. However, an incorrect diagnosis was made in 2 cases. One of these patients was first seen in the twentieth week of gestation complaining of acute right-sided pain with muscle spasm, rebound tenderness, fever, and leukocytosis. A preoperative diagnosis was made of acute appendicitis. Laparotomy revealed a twisted 9 cm. serous cystadenoma of the right ovary, which was removed.

In the other case, a patient with a very irregular menstrual history and progressively severe lower abdominal pain of several months' duration presented pelvic and abdominal findings strongly suggesting an abdominal pregnancy. X-ray studies were of no help. Laparotomy revealed an intrauterine pregnancy of 20 weeks' gestation and a 9 cm. solid ovarian tumor which microscopic examination revealed to be an extensive chronic edema.

TABLE IV. INCORRECT DIAGNOSIS

PREOPERATIVE DIAGNOSIS	SURGICAL FINDINGS	
Third Trimester.—		
1. Appendicitis	Twisted parovarian cyst	6 cm.
2. Abruptio placentae	Ruptured endometrial cysts	8 cm.
3. Uterine fibroid	Serous cyst	18 cm.
4. Abdominal pregnancy	Pseudomucinous cyst	20 cm.
Labor.—		
1. Transverse lie	Pseudomucinous cyst	15 cm.
2. Cervical fibroid	Bilateral dermoids, each	8 cm.
Puerperium.—		
1. Appendiceal abscess (sixteenth day post partum)	Infected parovarian cyst	7 cm.

C. Third Trimester (Table IV).—

In 4 patients, the existence of an ovarian tumor was established at or near term. In all 4 cases, the preoperative diagnosis had been erroneous.

One patient presented the typical picture of acute appendicitis. A twisted parovarian cyst, 6 cm. in size, was removed at laparotomy through a McBurney incision. Twenty-four hours later, the patient went into labor and delivered spontaneously from below.

The second patient was operated upon with a preoperative diagnosis of degenerating fibroid or possible abruptio placentae. Ruptured bilateral endometrial cysts were found and cesarean hysterectomy and bilateral salpingo-oophorectomy were performed with a living baby.

In a third patient, a preoperative diagnosis was made of term abdominal pregnancy. X-rays showed the baby to be in an oblique presentation but were of no further help. At laparotomy, a 20 cm. sized pseudomucinous cystadenoma of the ovary was removed and a term living baby delivered by cesarean section.

In a fourth patient, an elective cesarean section was performed because of a twin pregnancy complicated by what was thought to be a large cervical fibroid. An 18 cm. sized serous cystadenoma of the ovary was found and removed.

D. During Labor.—

Four patients had ovarian tumors obstructing the birth canal during labor. In none of these patients had the existence of an ovarian tumor been suspected prior to the onset of labor. In 2 cases, the true diagnosis was not established until laparotomy.

In one of these patients, a cesarean section was performed after 12 hours of labor because of failure of the presenting part to engage and pelvic and abdominal findings which suggested either an oblique presentation or twins. X-ray studies were not carried out. At laparotomy, a 15 cm. sized pseudomucinous cystadenoma of the ovary was found and removed. The baby, lying in normal position, was delivered by section.

In the other patient the dystocia was thought to be due to a large cervical fibroid and a cesarean section was performed without examination of the ovaries. Examination of this patient six weeks post partum revealed bilateral adnexal tumors which, at subsequent laparotomy, proved to be 8 by 8 cm. sized bilateral dermoid tumors.

E. Post Partum.—

In two cases, the ovarian tumors had not caused symptoms and were not diagnosed until the puerperium. One was correctly diagnosed as a twisted ovarian cyst on the tenth day post partum. The other patient developed lower right-quadrant pain and fever immediately post partum. On the sixteenth postpartum day, with a preoperative diagnosis of appendiceal abscess, laparotomy revealed an unruptured 7 by 5 cm. sized abscessed parovarian cyst.

F. Tumors Incidentally Found at Cesarean Section.—

In these 3 cases, the ovarian tumors had produced no symptoms and had not been recognized prior to cesarean section for other indications. Two of these tumors were corpus luteum cysts, 6 and 8 cm. in size. A third was an 8 cm. dermoid.

X-ray Findings

X-ray studies of the abdomen may be of considerable diagnostic help when the existence of an ovarian tumor is suspected during pregnancy. X-rays of the abdomen were made in 17 of the cases in our series. In 14, the x-ray findings aided in the diagnosis. Teeth or calcification were demonstrated in 5 of the 8 dermoid tumors. The existence of an extrauterine mass was demonstrated in 4 cases. X-ray confirmed the failure of engagement of the presenting part, showing the fetal head to be off to one side of the pelvis in several of the cases in which a tumor mass obstructed the pelvis during labor. In 1 of these, additional aid was offered by the showing of a tooth in the obstructing tumor. X-ray was particularly helpful in establishing the diagnosis of a large ovarian tumor, the size of a term pregnancy, by demonstrating the absence of a fetal skeleton in the tumor mass.

It is our opinion that x-ray studies of the abdomen are indicated wherever the presence of an ovarian tumor is suspected during pregnancy.

The Indications for Surgery

The indications for surgery are given in Table V.

TABLE V. INDICATIONS FOR SURGERY

TIME OF SURGERY	INDICATIONS		NO. OF CASES
First trimester	"Surgical abdomen"		9
Second trimester	Symptomatic tumors	12	17
	Asymptomatic tumors	5	
Third trimester	"Surgical abdomen"	2	8
	Obstruction birth canal	2	
	? Abdominal pregnancy	1	
	Tumor incidental at section	3	
Labor	Obstruction of birth canal		3
Post partum	Torsion of pedicle	3	7
	Asymptomatic tumors	3	
	Symptomatic tumor	1	
Post abortion	Asymptomatic tumor		1

A. First Trimester.—

In the first trimester, all 9 patients were operated upon because of the clinical picture of an acute abdominal crisis. In 5, a preoperative diagnosis had been made of ectopic pregnancy; in 4, a preoperative diagnosis of a twisted ovarian tumor was confirmed at surgery.

B. Second Trimester.—

In the second trimester, surgery was performed in 12 cases because of progressive lower abdominal pain in the presence of an increasingly tender adnexal tumor.

The persistence of an asymptomatic adnexal tumor, 6 cm. or larger, was the surgical indication in the remaining 5 cases.

C. Third Trimester.—

In the third trimester, all 8 operations were performed at or near term. In 2 cases, there was an "acute abdomen," one due to a twisted parovarian cyst and the other to ruptured bilateral endometrial cysts. The third patient with

obstruction of the birth canal, due to an 18 cm. serous cystadenoma, was electively sectioned prior to labor. In the fourth case, pregnancy was terminated electively by section at term because of an 8 cm. dermoid which obstructed the birth canal. This ovarian tumor had been diagnosed in the cul-de-sac at 16 weeks' gestation and kept under observation in the hope that the tumor would rise out of the pelvis as pregnancy progressed. The fifth patient, with a 20 cm. pseudomucinous cystadenoma complicating a term pregnancy, was sectioned electively because of a preoperative diagnosis of abdominal pregnancy.

In 3 other cases, the ovarian tumors were found incidentally at cesarean section for other indications.

D. During Labor.—

Cesarean section was indicated in 3 cases because of an ovarian tumor blocking the birth canal.

E. Post Partum.—

In the postpartum period, 7 patients were operated upon for ovarian tumors which had existed during pregnancy. In 2 cases, acute torsion of the tumors, which had been diagnosed in the first trimester and had remained asymptomatic, occurred 7 days and 6 months post partum, respectively, requiring immediate surgery. In another case, an infected parovarian cyst was removed 16 days post partum.

The persistence of an adnexal mass post partum was the surgical indication for removal in 3 cases. One of these tumors, a 10 cm. dermoid, had obstructed the birth canal during labor, had been pushed out of the pelvis to permit spontaneous vaginal delivery of the baby, and was removed electively 3 months post partum. The second, a 9 cm. dermoid, which had been diagnosed in the first trimester, remained asymptomatic during pregnancy, labor, and the puerperium, and was removed electively 4 months post partum. The third, an 8 cm. serous cystadenoma diagnosed in the first trimester, was removed 8 weeks post partum. The tumor had remained asymptomatic during pregnancy but the patient had developed a fulminating toxemia and delivered a stillborn infant at 32 weeks.

F. Post Abortion.—

In one patient a 10 cm. fibroid was diagnosed at 14 weeks' gestation. Spontaneous abortion occurred at 16 weeks. The ovarian tumor was removed 4 months post abortion.

Results of Surgery

The results of surgery are shown in Table VI.

TABLE VI. RESULTS OF SURGERY

TIME OF SURGERY	NO. OF CASES	FETAL SURVIVAL	MATERNAL SURVIVAL
First trimester	9	6	9
Second trimester	17	15	17
Third trimester	7	7	7
Labor	4	3	4
Post partum	7	6	7
Post abortion	1	0	1
Gross fetal mortality	45	37	45
Total	18%	Gross maternal mortality	0

1. Maternal.—

There were no maternal mortality and no significant maternal morbidity from the surgery for the ovarian tumors. The abdominal wounds healed well and successfully withstood labor and vaginal delivery in 21 patients operated upon in the first and second trimesters.

2. Fetal.—

There were 37 live babies in the 45 pregnancies, giving a gross fetal mortality rate of 18 per cent.

A. First Trimester.—In 9 patients operated upon in the first trimester, 3 pregnancies were lost. Two patients miscarried one and three weeks postoperatively. Each had had symptoms of a threatened miscarriage with vaginal bleeding one to three weeks prior to surgery. One had a dermoid cyst of 8 cm. and the other a serous cystadenoma of 8 cm. with a twisted pedicle. The third patient had incarcerated 12 cm. sized bilateral lutein cysts associated with a hydatid mole. The cysts in this patient were freed from the pelvis at surgery, the mole being aborted spontaneously several days later.

B. Second Trimester.—In the 17 patients who underwent surgery in the second trimester, 15 went to term and delivered living babies. Of the 2 pregnancies that were lost in the second trimester, 1 was delivered at 34 weeks at the time of hysterotomy and bilateral salpingo-oophorectomy for large bilateral Kruckenberg tumors secondary to an extensive gastric carcinoma with widespread abdominal metastases. The other patient miscarried at 24 weeks, 2 days after the surgical removal of a 9 cm. ovarian tumor which on microscopic examination showed extensive chronic edema.

C. Third Trimester.—There was no fetal loss in the 7 patients operated upon in the late third trimester.

D. Labor.—One of the 4 patients operated upon in labor had a stillborn infant. This stillbirth occurred in a case in which an asymptomatic 8 cm. corpus luteum cyst was found incidentally at cesarean section. The section was performed after a prolonged labor because of multiple fibroids which had blocked the descent of the fetus. The fetal heart beat had been lost prior to the section.

E. Post Partum.—Of the 7 patients whose ovarian tumors had been present during pregnancy but were not removed until the puerperium, all but one had given birth to living babies. This one pregnancy had terminated at 32 weeks with a stillborn infant, the mother having developed a severe toxemia with an abruptio placentae.

F. Post Abortion.—A 10 cm. fibroma of the ovary was removed 4 months post abortion in 1 patient. The fibroma had been diagnosed at the fourteenth week of gestation and the spontaneous miscarriage had occurred two weeks later in the sixteenth week.

Progesterone Therapy

Of the 21 patients operated upon in the first and second trimesters who went on successfully to term, only 9 received any form of postoperative progesterone therapy. Only 1 patient received more than 10 mg. of progesterone

intramuscularly daily. The 2 patients who aborted at 1 and 3 weeks after surgery had had symptoms of a threatened abortion with vaginal bleeding for several weeks prior to surgery. Neither received postoperative progesterone. Whether this hormonal therapy would have changed the ultimate outcome is problematical.

Surgical Techniques

There was no correlation between the outcome of the pregnancy and the variety of types of anesthesia and surgical techniques employed by the different operators. In most instances, a unilateral oophorectomy was performed except in those at or near term on whom a cesarean section was also performed. In a few cases, because of the nature of the pathology, additional pelvic surgery was carried out.

Special Case Reports

Several cases encountered in this series presented features of unusual interest.

1. Unusually Large Ovarian Tumor.—

A 24-year-old housewife, a private patient of one of us, missed two menstrual periods. There had been no previous pregnancies. Abdominal examination revealed a cystic enlargement the size of a term pregnancy. No fetal parts could be palpated and no fetal heart tones were heard. Pelvic examination revealed the cervix to be soft and it was thought that the corpus, approximately the size of a 2½ months' pregnancy, could be felt pushed to the left by a cystic mass bulging into the pelvis. X-ray examination of the abdomen showed a soft-tissue mass filling the abdominal cavity, but no fetal skeleton. A frog test for pregnancy was positive. A diagnosis was made of a large ovarian tumor complicating a 10 weeks' intrauterine pregnancy. At laparotomy in the thirteenth week of gestation, a 35 cm. smooth-walled left ovarian cyst was found bulging into the pelvis and extending upward to the diaphragm. A trocar was inserted into the cyst, a purse-string suture through the cyst wall drawn tightly about it to prevent spillage of the cyst contents, and 6,000 c.c. of fluid withdrawn, collapsing the tumor. A left salpingo-oophorectomy was then performed. Pathological examination of the tumor showed a serous cystadenoma. The patient's convalescence was uneventful, progesterone 10 mg. intramuscularly being given daily for the first 3 postoperative days. The pregnancy continued normally to term and a spontaneous vaginal delivery of a living infant was accomplished uneventfully.

2. Bilateral Krukenberg Tumors and Pregnancy.—

A 30-year-old housewife was admitted to the hospital in the sixth month of her third pregnancy because of a rapid increase in the size of the abdomen, weight loss, hematemesis, and melena. She had been on a medical ulcer regime for the preceding year. Abdominal examination revealed a uniform enlargement to the size of a term pregnancy, the uterus arising to the umbilicus with evidence of considerable ascites. On vaginal examination, the soft cervix was displaced high behind the symphysis by a grapefruit-sized, firm, fixed mass in the cul-de-sac which did not seem to be incorporated into the rectal wall but was partially attached to the uterus although not a part of it. A diagnosis was made of an ovarian malignancy complicating a 6 months' intrauterine pregnancy and partial intestinal obstruction. At laparotomy, a 19 cm. solid tumor of the left ovary and a 7 cm. solid tumor of the right ovary were found together with a large primary carcinoma of the stomach and generalized carcinomatosis of the intestinal, mesentary, and retroperitoneal lymph nodes. The 6 months pregnant uterus showed no metastatic involvement. A hysterotomy, bilateral salpingo-oophorectomy, and appendicostomy were performed. The pathological report of the ovaries showed typical Krukenberg tumors. The previable infant died after 36 hours. The mother died 6 months later of generalized carcinomatosis.

3. Adenocarcinoma of the Ovary.—

This 25-year-old patient was admitted to the hospital in the fourteenth week of her first pregnancy because of a general abdominal pain of 5 weeks' duration which had localized in the left lower quadrant. A large tumor of the left ovary had been found on pelvic examination. At laparotomy, a 11 cm. cystic, smooth-walled, left ovarian tumor was found, together with a 3½ months pregnant uterus. As soon as the removed ovarian tumor was opened, it was found to be filled with soft, friable, cauliflower-like, papillomatous proliferating tissue which frozen section demonstrated to be adenocarcinoma. The right ovary appeared uninvolved and there was no evidence of metastasis. The surgeon reasoned that if the carcinoma was limited to the removed ovary, no further surgery was necessary. The patient, a primigravida, was very anxious to have this baby and, if microscopic metastasis had already occurred, more radical immediate surgery would not only sacrifice the baby but even at best offer a poor prognosis for cure of the malignancy. Thus the abdomen was closed after a left salpingo-oophorectomy was performed. Permanent microscopic section revealed an adenocarcinoma, Grade II, of the ovary with a limited invasion of the capsule with tumor cells. The patient's convalescence and subsequent course during her pregnancy were uneventful. Shortly before term she was again admitted to the hospital and a living normal infant delivered by cesarean hysterectomy and right salpingo-oophorectomy. At surgery, there was no evidence of recurrence or metastasis of the carcinoma. Careful microscopic examination of the uterus, tube, and ovary showed no carcinoma. The patient is living and well five years later.

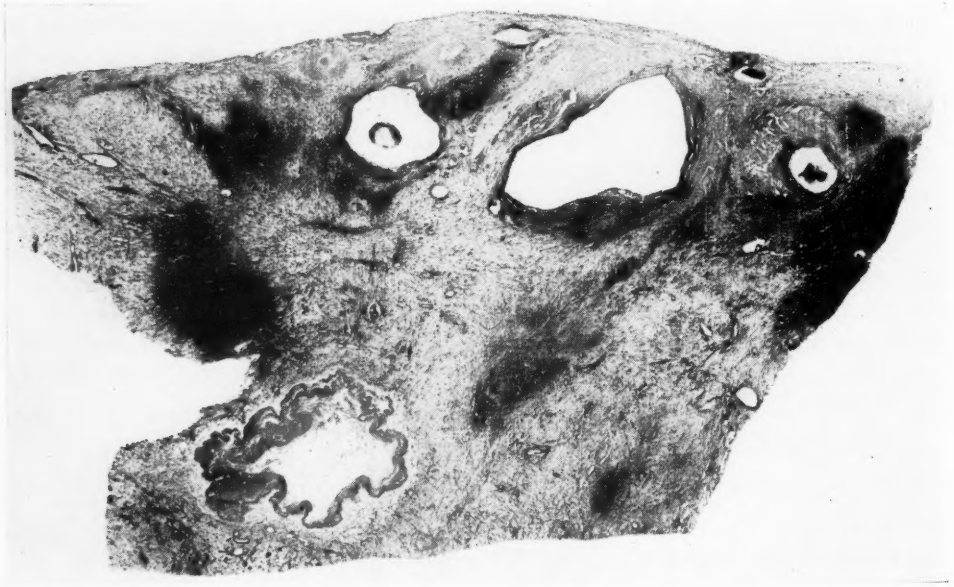

Fig. 1.—Extensive chronic edema of the ovary. Only normal structures are shown with extensive intracellular fluid edema separating the normal ovarian tissues. Dilated lymph channels are seen together with corpora albicantia and several cystic follicles.

4. Extensive Chronic Edema of the Ovary.—

A 22-year-old para ii had been amenorrheic for some 10 months and complained of an increasing pain in the right lower quadrant. Pelvic and abdominal findings were most difficult to interpret and x-ray studies were inconclusive. The general consensus of those who examined the patient was in favor of an abdominal pregnancy. In an attempt to clarify the diagnosis further, a small amount of Iodochlorol was injected into the cervical canal. X-ray now revealed an intrauterine pregnancy of 20 weeks with a large adnexal tumor. At laparotomy, a 9 cm. solid smooth-walled tumor of the left ovary was found and removed. The patient aborted the day following surgery. Microscopic examination of the ovarian tumor

revealed a unique pathologic picture. The entire tumor consisted of the normal ovarian structures separated by extensive edema* (Fig. 1). No other case of such extensive edema of the ovary during pregnancy could be found in the literature.

Comment

An ovarian enlargement of less than 6 cm. is frequently encountered in early pregnancy. Usually, this is due to a cystic corpus luteum which in most instances disappears as pregnancy advances. However, when rupture occurs with intra-abdominal hemorrhage, differential diagnosis from ectopic pregnancy cannot be made and laparotomy is indicated. In many instances, removal of the corpus luteum will not interrupt the pregnancy but postoperative progesterone therapy is indicated.

An ovarian tumor, 6 cm. or larger, found in the first trimester is usually a neoplasm and should be removed early in the second trimester unless twisting of a pedicle or rupture necessitates immediate surgery. Our best results were in operations performed in the early second trimester. It is impossible to differentiate the various tumors preoperatively with the exception of roentgenologic demonstration of characteristic calcification in the dermoids.

In two instances, patients who had ovarian tumors diagnosed in the first trimester went through pregnancy, labor, and the early puerperium uneventfully, only to have torsion of the pedicle necessitating immediate surgery on the seventh postpartum day and at 6 months post partum.

Patients operated upon for ovarian tumors in the first and second trimesters may be permitted to go into labor and be delivered vaginally without fear of wound disruption. This was demonstrated in all 21 patients who were operated upon in the first two trimesters and went to term.

Diagnosis of ovarian tumors in the third trimester is increasingly difficult because of the further enlargement of the uterus and the ever present danger of pathologic changes in the cyst, and dislodgement of the fetus by the cyst. All four cases in this series were incorrectly diagnosed.

Diagnosis of an ovarian tumor 8 cm. or larger at term warrants cesarean section and removal of the tumor.

Ovarian tumors obstructing the birth canal are subjected to considerable pressure during labor. In the presence of a ruptured dermoid, peritonitis is very likely to occur, a fact demonstrated to one of us at autopsy some years ago.

We believe that in the case of the ovarian tumor obstructing the birth canal during labor, cesarean section plus removal of the tumor is the safest form of management. To displace the ovarian tumor upward manually is to risk rupture of the tumor. To attempt to collapse the tumor by a needle or trocar through the cul-de-sac permits too great a possibility of intraperitoneal spill of tumor contents. Four of the five ovarian tumors obstructing the birth canal in our series were dermoids.

The possibility of malignancy in ovarian tumors complicating pregnancy must always be considered. Each case must be individualized and the decision as to management must be based on a careful consideration of all the various factors involved.

*The microscopic slides were reviewed by Dr. Emil Novak who agreed with this interpretation.

Summary

1. Forty-five cases of surgically proved ovarian tumors 6 cm. or larger complicating pregnancy have been collected from four Indianapolis hospitals.

2. The methods of diagnosis are evaluated and errors in diagnosis (36 per cent) are discussed.

3. The types of complications, the surgical indications, and the results are presented.

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Discussion

DR. REYNOLD HAAS, Ann Arbor, Mich.—The incidence of approximately 1:2,200 deliveries is considerably lower than that of 1:316 which I reported 4 years ago, but is more in keeping with the average of reports in the literature. Undoubtedly we all miss a fair number of these tumors.

The difficulties of diagnosis of this complex are well appreciated. I would support the authors' statement, "It may be impossible to differentiate ectopic pregnancy from smaller ovarian tumors, especially a bleeding corpus luteum cyst with intraperitoneal hemorrhage." Actually, the important thing here is the diagnosis of the intraperitoneal bleeding, since it usually demands surgery, whatever the source. However, it is necessary to differentiate between cystic ovarian tumors and uterine fibroids. If there is reasonable doubt in a given case, careful examination under anesthesia should be utilized, since the cyst may well require operation, while the fibroid usually will not.

The ovarian tumor created by pure edema is an interesting—and exceedingly rare—occurrence.

Several problems regarding management are brought out by the case descriptions. In the patient operated upon near term and found to have bilateral ruptured endometrial cysts, one wonders what other circumstances justified a cesarean hysterectomy and bilateral salpingo-oophorectomy. My preference would have been to do the cesarean section, and then bilateral partial ovarian resection if this were possible.

Another patient, sectioned for a presumed obstructing cervical fibroid, was found six weeks later to have bilateral dermoids requiring a second laparotomy. This emphasizes the necessity for routine inspection of the abdominopelvic structures—particularly the ovaries—at the time of any cesarean section.

A third patient, operated upon at 3½ months' gestation, had a unilateral salpingo-oophorectomy for what proved to be an adenocarcinoma without apparent spread. Six months later, a cesarean hysterectomy with removal of the remaining tube and ovary was carried out. I believe some of us might have been content with the first operation in this young patient, or at most would have explored the pelvis and abdomen at cesarean section, and would have spared the uterus and remaining tube and ovary when they were found to be grossly normal.

The authors state that "in most instances a unilateral oophorectomy was performed," and it is possible that the extent of pathology made this necessary in many cases. However, I wish to emphasize that the possibility of partial resection, with preservation of ovarian tissue, should always be kept in mind, and it can often be accomplished if one can take the time for careful dissection.

Dr. Gustafson also stated, "Diagnosis of an ovarian tumor 8 cm. or larger at term warrants cesarean section and removal of the tumor." With this statement I would take exception. Not all 8 cm. tumors would be of such nature or location as to cause trouble during labor and delivery. It is commonly accepted that cesarean section babies may have

a survival hazard somewhat greater than those delivered vaginally. Furthermore, depending on one's philosophy, the cesarean section may make the patient an obstetric cripple. It seems that at least some such tumors might well be observed until after delivery, and taken care of at a later date.

It is interesting that the authors found so many cases—over 50 per cent of the series—in which the cysts produced such symptoms as to demand prompt surgery. In contrast, our own group revealed only 2 patients out of 25 who had symptoms suggesting torsion of the cyst. This emphasizes the great variability of behavior of ovarian cysts during pregnancy.

From reports such as this, it is evident that we need better detection and differentiation of ovarian tumors complicated by pregnancy. When this is achieved, management will be simpler to determine.

DR. HUGH HAMILTON, Kansas City, Mo.—The presentation serves to point up the doctrine that as obstetricians and gynecologists we should not develop "gun-barrel vision" and content ourselves with diagnosing and treating the single, obvious presenting problem, in these cases, pregnancy. Rather, we should view the entire woman as an entity and be alert to treat any and all other attendant disorders. Second, it serves to emphasize the fact that when a disease process is present in a pregnant woman, that disease process should be given definitive therapy. For example, I feel that the wretched statistics on the results of the treatment of breast carcinoma in pregnancy are in fact due to failure to make early diagnosis and failure to institute early and definitive therapy.

The necessity of early, careful examination of pregnant women is clearly demonstrated in this problem, as it is difficult to make an accurate diagnosis in the last half of pregnancy. McKerron's statistics on the rate of abortion following surgery for ovarian tumors in pregnancy show that it is four times as safe to operate upon these women from the thirteenth to the twentieth week as it is to operate earlier or later. Therefore, it is important to get them in early for examination and institute surgery at this time.

Since our previous report of 21 cases of surgically proved ovarian tumors complicating pregnancy, we have had 5 more such cases. We have continued to use progesterone therapy preoperatively and postoperatively, but I am not at all convinced of its efficacy as I was five years ago. We had had no maternal mortality then or now except one death from metastatic carcinoma in a patient operated upon post partum who died 8 months later. We had had no patient abort in the first series. Now we have had one who aborted postoperatively. This girl had aborted at 20 weeks' gestation previously, and at postpartum examination we had found a 7 cm. ovarian tumor. She did not come back to arrange for her suggested surgery, and next time reported to the office when she was 12 weeks pregnant, giving the history of scant intermittent bleeding for the previous 10 days. She was sent to the hospital and after 7 days' rest in bed a 9 cm. dermoid cyst of the left ovary was removed. She aborted 48 hours later.

In the matter of examination of the women, let me emphasize the necessity for gentleness. The next to the last patient we had was a young woman whom we had previously treated for infertility. After a lapse of several months she reported to the office at 7 weeks' gestation and upon examination, in addition to the intrauterine pregnancy, there was a 7 to 8 cm. left ovarian tumor that lay anterior to the broad ligament. It was quite freely movable. One of my partners and I were quite intrigued and each demonstrated to the other how this tumor could be shoved about. We arranged to operate upon her seven weeks later and she went home. She called us in an hour with left lower quadrant pain and we hospitalized her. Six hours after the examination we removed a 7 cm. dermoid cyst with torsion of the pedicle, which torsion I am certain was caused by two meddlesome physicians. At this point it should be emphasized that in removing a cyst with torsion of the pedicle, the pedicle should be clamped at its base, for severance after the torsion is untwisted increases the risk of embolus.

Here is one question that might be raised in the management of Dr. Gustafson's case of carcinoma of the ovary. The patient was operated upon in the fourteenth week of gestation and the carcinoma was still apparently contained within the cyst wall. At the thirty-

eighth or thirty-ninth week she was subjected to cesarean section, hysterectomy, and removal of the other ovary. The only reason for such surgery would be the reduction of the possibility of metastatic growth. I feel that in the intervening 24 or 25 weeks, especially under the influence of pregnancy, it is quite probable that any metastasis would have long since established itself and been growing. The die was cast in this case when the decision to let the pregnancy continue was made at 14 weeks' gestation. We have two similar cases in our series, where no further surgery was performed, the pregnancy was allowed to go to term and delivery, and both women are alive and well 5 and 6 years later. One of these women has had 3 subsequent children.

If one feels that there should be more definitive therapy, the pregnancy should be interrupted at that time, and the complete operation should be performed at that time. Then, as suggested by Mengert, in the postoperative care, surface peritoneal implants might be helped by the usage of intraperitoneal radioactive gold.

I also would like to ask Dr. Gustafson what they accomplished by doing a cesarean section at twenty-eight weeks on the patient with the bilateral Krukenberg tumor.

DR. SIMON V. WARD, New Orleans, La.—I realize that these cases presented by Dr. Gustafson are not his own but are a collection from Indianapolis.

I was interested particularly in Dr. Gustafson's case report of the bilateral Krukenberg. I believe there are only three cases of Krukenberg tumor during pregnancy reported in the literature, as reviewed by Drs. Dougherty and Lund, which he referred to in his paper.

We have one case which is in the process of preparation for publication. This case of Krukenberg tumor was discovered in the twelfth or thirteenth week of pregnancy, and the patient was operated upon at that time. The tumor was removed. She was allowed to continue to term. However, during that time a gastroenterostomy was necessary to maintain an open passage, because her generalized stomach cancer was obstructive. She was delivered, and I believe she is the first with a Krukenberg tumor to be reported on who delivered a live baby.

I want to ask Dr. Gustafson what his opinion is about the therapeutic abortion that was done at that time. We did not feel that the pregnancy influenced the course of the carcinoma of the stomach in our case. The patient died three or four months after delivery.

DR. C. GORDON JOHNSON, New Orleans, La.—I was quite surprised to find that in reviewing very carefully our records on the Tulane Service at Charity Hospital, which represents 40 per cent of the population at Charity, there were only 4 cases of solid ovarian tumors occurring during pregnancy. These 4 occurred in approximately 40,000 deliveries on the Tulane unit over a ten-year period.

Dr. Dougherty and Dr. Lund, on the Louisiana State University service, who also have 40 per cent of the population at Charity, had reported only 6 cases for ten years prior to 1939. My ten-year period goes back to 1943. Of these 4 cases, 3 were dermoids, one was a solid fibroma. In one instance only was it necessary to operate for an obstruction to labor. Two of the patients were operated on because of severe abdominal pain that occurred in the second trimester. The fourth case was found at the same time that a cesarean section was done for disproportion.

The 2 patients operated on during the second trimester had uneventful pregnancies and uneventful deliveries.

I am at a loss to explain why we do not have more solid ovarian tumors than we apparently do have; but, taking the entire Hospital, with the LSU service, the independent service (which takes care of 20 per cent of the population), and our own Tulane service, over a ten-year period we perhaps would have seen only 12 or 14 in over 100,000 deliveries, because at the present time we are averaging close to 12,000 deliveries on the obstetrical service.

DR. C. PAUL HODGKINSON, Birmingham, Mich.—I would like to mention a case of a large thecoma which was removed on the fifth postpartum day from a very obese

Negro patient. We did not make this diagnosis prior to delivery, either. This tumor was of great size. It measured 40 cm. in its greatest diameter. This type of tumor appears to offer an additional hazard to the pregnant patient.

The venous engorgement and dilatation of the vessels over the surface of this tumor were tremendous. I am sure that several of the veins measured 2 cm. in diameter.

We were greatly impressed by this venous engorgement, and have looked up the literature on thecomas associated with pregnancy. There are only 8 reported that we could find. Three of the patients delivered with the coexistent tumor. However, 2 of the patients died of intraperitoneal hemorrhage from rupture of one of the veins over the surface of the tumor.

I wonder if this venous engorgement is unique to this particular type of tumor, or whether it is caused by the pregnancy alone. At least we feel from our observation of this case, and from what the literature tells us, that perhaps there is an additional hazard in pregnancy if this particular type of tumor is present.

I wonder if Dr. Gustafson has anything to say about this type of tumor in pregnancy.

DR. GUSTAFSON (Closing).—Dr. Haas spoke about the case of bilateral endometrial cysts. I might say that that particular case, the ovarian carcinoma of pregnancy, and the Krukenberg tumors, were cases that we did not see personally.

I was very happy that they got this result with the ovarian carcinoma of pregnancy. I am afraid that, if it had been my case, there would have been no baby. Certainly, if it were my daughter with a proved carcinoma of the ovary, I would be in favor of interruption of the pregnancy, with a total hysterectomy and bilateral salpingo-oophorectomy right then and there.

What are you going to do when the patient is not pregnant? A few months ago I removed a pseudomucinous cyst which looked grossly to be benign, and it was only after many, many sections had been taken that they found one or two areas of carcinoma. We operated again ten days later and removed the other ovary and the tubes and uterus. That would be my thought as far as the treatment of ovarian carcinoma complicating pregnancy is concerned.

Nevertheless, this young lady has a baby that she would not have had.

We believe that, with an 8 cm. tumor blocking the birth canal, the patient should be delivered by cesarean section, and the tumor removed at that time, if the diagnosis has been made. I was convinced of this a good many years ago when at autopsy on a patient at General Hospital, who died from puerperal peritonitis, we found a ruptured dermoid which had been the source of the infection.

How much pressure the tumor is going to have during labor, the dangers of rupture, and the additional danger of hemorrhage, which Dr. Hodgkinson mentioned, because of the large vessels that might be present on the tumor, are important considerations. Personally, I have had no experience with thecomas complicating pregnancy.

Dr. Hamilton asked what was accomplished by the hysterotomy for Krukenberg tumor. I do not think anything was accomplished. I might say that this woman, in addition to her tumor, also had partial intestinal obstruction at that particular time, and at the operation when the hysterotomy was done an appendicostomy was performed. I think it was probably necessary to do something, although, as I say, we had no connection at all with that particular case.

Dr. Ward and Dr. Gordon Johnson asked questions: As far as the increased incidence of tumors in private practice and in ward service such as at Charity are concerned, may it not be that in private practice more of these patients with tumors come to the doctor earlier, possibly, than they do in the prenatal clinics in the large charity hospitals?

HIGH OXYGEN AND HYALINE-LIKE MEMBRANES*†‡

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PULMONARY hyaline membranes in newborn infants remain a source of curiosity and controversy, in regard to their nature, etiology, diagnosis, and pathologic significance. Recently, De and Anderson[5] have reviewed this important subject in extenso. These pink-staining membranes are present in a wide variety of clinical and experimental pulmonary conditions. Their staining characteristics are quite similar, thus inferring a common etiology for all types. The chief microscopic difference is the presence of atelectasis in the lung of the newborn. The latter suggests a dissimilarity between the various types of membranes. It is also believed that atelectasis in the infant may play the predominantly lethal role while the pink-staining pulmonary membranes are eosinophilic herrings.[14]

There has been a long-lasting and understandable reluctance to accept high oxygen as an injurious agent even though an amazing literature has accumulated on this topic. Stadie's[16] and Bean's[1] exhaustive reviews of oxygen poisoning in 1944 and 1945 amply explain why such skepticism persists. One is almost forced, however, to conclude that high oxygen at sea level pressure breathed over long periods in man or animals produces pulmonary damage, one manifestation of which is hyaline-like membrane formation.[8] There is presently a growing clinical acceptance of high oxygen as a causative or aggravating agent in various diseases of the newly born premature infant.[15] The purpose of this study is to explore experimentally and clinically the relationship of high oxygen and hyaline membranes which continues to shroud the problem of premature neonatal death.

Experimental Pulmonary Hyaline Membranes

Control Animals in Air.—

Thirty adult guinea pigs were killed to study normal pulmonary histology and to serve as controls for the high oxygen experiments. All were young adults of both sexes obtained from the same colony and killed in room air at 630 mm. Hg barometric pressure.

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†Part of this material appeared in an unpublished thesis submitted to the Faculty of the Graduate School of Medicine, University of Colorado, in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology by Lloyd V. Shields, M.D.

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Seventy-five per cent of all so-called normal lungs showed chronic granulomatous infection of mild, moderate, or severe degree. This infection was diffuse or patchy in character and frequently associated with perivascular and peribronchiolar round-cell infiltration. Traces of hyaline membranes were found occasionally in some areas of chronic infection.

Control Animals in Oxygen.—

Ten guinea pigs were exposed to 95 to 98 per cent oxygen at 50 per cent relative humidity, 78° F. and 760 mm. Hg barometric pressure. The animals in this experiment, as well as those in all subsequent experiments, were placed in a sealed plastic chamber under similar environmental conditions and offered food and water. A continuous baffled flow of commercial dry oxygen at 5 to 10 L. per minute was passed through the chamber to maintain 760 mm. Hg barometric pressure and to wash out excess carbon dioxide. No determinations of CO_2 were made. Analyses for oxygen concentrations were made at regular intervals.

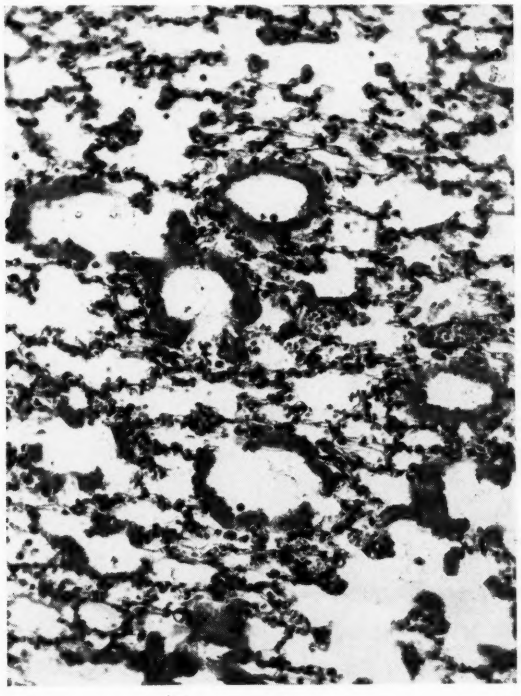

Fig. 1.—High oxygen hyaline membranes. This guinea pig died spontaneously after 45 hours' exposure to 98 per cent oxygen. The lung shows one to two plus "ductal" membranes. Note the absence of atelectasis, edema, hemorrhage, and infection.

Most animals became anorexic after 25 to 50 hours' exposure and lost an average of 50 grams in body weight. Clinically, they showed respiratory distress during the latter half of an experiment. At autopsy, the lungs invariably looked like liver and sank in formalin. Seventy-five per cent of the animals exposed to high oxygen concentrations in this and previous experiments[3]

showed pulmonary hyaline membranes to the extent of one plus or more (Fig. 1). The associated, and perhaps more important, pulmonary pathology of oxygen poisoning consisted in varying degrees of vascular engorgement, edema, hemorrhage, epithelial necrosis, and inflammatory reaction.[6]

Regression of Experimental Hyaline Membranes.—

Forty-two young adult guinea pigs were exposed to 98 per cent oxygen. Groups of eight were placed in oxygen for 4, 8, 16, 32, and 64 hours. The surviving animals were removed and killed at regular intervals of one day and 1, 2, 3, 4, and 5 weeks.

Well-developed hyaline membranes usually appeared between 32 and 64 hours. In the surviving animals, removed from oxygen and killed at regular intervals, the acute pulmonary process frequently cleared within one day and hyaline membranes which were present in at least three-fourths of the guinea pigs disappeared within two weeks. Surviving animals showed little histological evidence of residual or permanent lung damage five weeks after exposure.

Effect of Humidity on Experimental Hyaline Membranes.—

Ten guinea pigs were exposed to 98 per cent oxygen at a relative humidity of 20 to 30 per cent. Another ten guinea pigs were exposed to high oxygen at an average humidity of 95 per cent. These relative humidities were obtained by increasing the rate of oxygen flow or by aerosolizing water. The pulmonary pathology in both series consisted of vascular engorgement, epithelial injury, edema, infection, and one to three plus hyaline membranes. Changing the relative humidity in these experiments did not appreciably alter the pulmonary pathology of oxygen poisoning.

Effect of Hyaluronidase on Experimental Hyaline Membranes.—

Ten guinea pigs were exposed to hyaluronidase (Wydase*) aerosolized by oxygen in the Vapojette† at the average rate of 1 unit or 1 c.c. per hour. All lungs showed marked epithelial injury, together with extensive hyaline membranes. Aerosolized hyaluronidase in these concentrations was a potent agent in promoting epithelial necrosis and experimental pulmonary hyaline membranes (Fig. 2).

Effect of Trypsin on Experimental Pulmonary Hyaline Membranes.—

Ten guinea pigs were exposed to a continuous fog of trypsin using 3 c.c. (125,000 units Tryptar‡) per hour and another ten animals to an intermittent mist of trypsin, using the same concentration every three hours. The continuous administration of Tryptar was also epitheliolytic while the intermittent administration of Tryptar appeared a little less injurious. In the presence of aerosolized trypsin, experimental membranes were more uniform in distribution and were associated with considerable necrosis and hyalinization of the bronchial tree.

*Supplied by Wyeth Incorporated, Philadelphia, Pa.
†Supplied by Air Shields, Incorporated, Hatsboro, Pa.
‡Supplied by The Armour Laboratories, Chicago, Ill.

Effect of "Wetting Agents" on Experimental Hyaline Membranes.—

Ten guinea pigs were placed in a continuous mist of 0.2 per cent Duponal C* and 98 per cent oxygen. Ten others were exposed to a continuous fog of 0.1 per cent Alevaire† and 98 per cent oxygen. In these concentrations, Duponal C (0.2 per cent) behaved in a highly irritating fashion, producing marked pulmonary epithelial injury, edema, and inflammatory reaction, while Alevaire (0.1 per cent) was associated with much less epithelial damage and very little pulmonary hyaline membrane formation (Fig. 3).

Ten guinea pigs were placed in a continuous aerosol of 75 per cent ethyl alcohol. The noteworthy pathologic finding was the relative absence of pulmonary hyaline membranes and the presence of extensive edema.

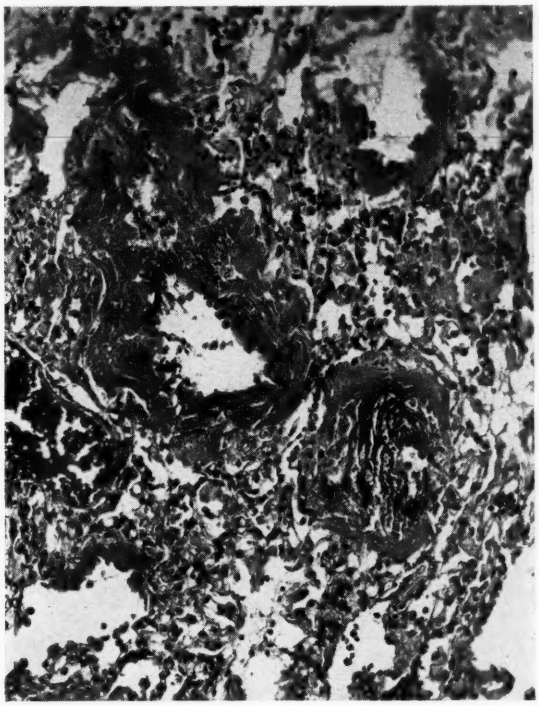

Fig. 2.—Hyaluronidase aerosol. This guinea pig died spontaneously in high oxygen after 88 hours of aerosolized hyaluronidase (76 units or 76 c.c. of Wydase). The lung shows marked epithelial necrosis and three to four plus hyaline membranes.

Effect of Amniotic Fluid and Thromboplastin on Experimental Membranes.—

Ten guinea pigs were exposed to 98 per cent oxygen in a mist of fresh amniotic fluid. Ten were given intermittent 5 c.c. aerosols of thromboplastin for a total dose of 80 c.c. in 80 hours. Neither amniotic fluid nor thromboplastin aerosols affected the amount of hyaline membrane formation. The oxygen-induced pulmonary pathology associated with the inhalation of amniotic fluid or thromboplastin was not unlike that of aerosolized water.

*Supplied by E. I. Du Pont de Nemours & Co., Wilmington, Del.
†Supplied by Winthrop-Stearns, Inc., New York, N. Y.

Effect of Therapeutic Doses of ACTH on Experimental Hyaline Membranes.—

Five male guinea pigs were given 5.0 mg. per kilogram per 24 hours of ACTH in divided doses every six hours. Five male pigs were given 8.0 mg. per kilogram per 24 hours of ACTH in divided doses every six hours. The therapeutic response was checked in each animal by the Thorn test. All showed an average reduction in circulating eosinophils of 50 per cent. The average duration of life was somewhat less in the ACTH-treated animals than in an equal number of controls. The pulmonary pathology was characterized by an increased inflammatory reaction and a large amount of hyaline membrane formation.

Fig. 3.—Alevaire aerosol. This animal was exposed to a continuous aerosol of 0.1 per cent Alevaire and died spontaneously in oxygen after 72 hours. There was relatively little pulmonary membrane formation. This section is also representative of the effect of 75 per cent ethyl alcohol aerosol.

Effect of Steroid Hormones on Experimental Hyaline Membranes.*—

Ten guinea pigs were given estrogens in oil and water in doses of 5.0 to 10.0 mg. per kilogram of body weight. Ten were injected intraperitoneally with 100 mg. of chorionic gonadotrophin, followed by 50 mg. intramuscularly of progesterone in oil. Twenty were injected similarly and used as controls. The experimental animals that died in 98 per cent oxygen showed an extensive amount of pulmonary pathology. Controls killed in air after 60 hours were normal.

The female guinea pigs given any female sex hormone died rapidly (17 hours) when exposed to 98 per cent oxygen. The predominant pulmonary

*Proluton, supplied by Schering Corporation, Bloomfield, N. J.

pathology in these animals consisted of massive vascular engorgement and hemorrhage.

Male guinea pigs given oil- and water-soluble estrogens, then exposed to 98 per cent oxygen, died after 56 hours with the usual lung findings of oxygen injury.

Female animals given either hormone, but exposed to 98 per cent oxygen after a 24 hour delay, reacted to oxygen poisoning in the usual way, dying within 50 to 100 hours after exposure.

Animals of either sex given progesterone and chorionic gonadotropin and then exposed to 98 per cent oxygen died rapidly (14 to 20 hours) and displayed the most violent type of pulmonary vascular disruption encountered in any oxygen experiment (Fig. 4).

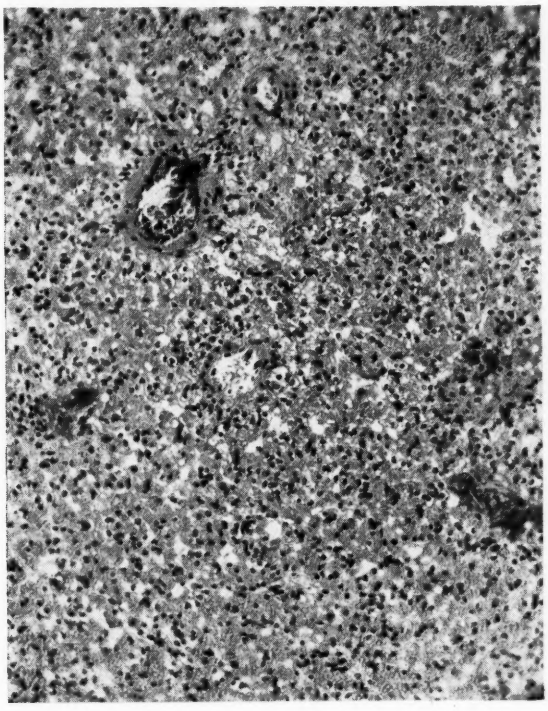

Fig. 4.—Chorionic gonadotrophin and progesterone effect. This female guinea pig, given 100 mg. of chorionic gonadotrophin intraperitoneally, followed by 100 mg. of progesterone intramuscularly, died spontaneously in high oxygen after 12 hours. The lungs show massive vascular engorgement, hemorrhage, epithelial necrosis, and clumps of bacteria. This section is also representative of estrogen effect in the female guinea pig.

Premature Infant Hyaline Membranes

The clinical features surrounding the mother and the premature infant with hyaline membrane disease are fairly well understood. Pregnancy is usually terminated vaginally. Too frequently, though, a premature infant succumbs with hyaline membranes who has been delivered by cesarean section. Careful evaluation of the mother's history does not always reveal a complication which can be associated with the premature onset of labor. The majority of delivered infants weigh between 1,000 and 2,000 grams, are in poor condi-

tion at birth, develop intermittent dyspnea and cyanosis while in or out of oxygen, and usually die within 96 hours. Some babies, strongly suspected clinically of having pulmonary hyaline membrane disease, apparently survive.

From July 1, 1948, to June 30, 1953, complete clinical and pathological information was available for a comparative study of 40 premature infants, 23 with hyaline membranes and 17 without. In summary, no specific maternal complication could always be determined as the cause of premature delivery and subsequent hyaline membrane disease. Many of the mothers in both groups had similar complications resulting in premature delivery. In the hyaline membrane group, five infants were delivered by cesarean section, the indications being repeat section, sarcoma, carcinoma, premature separation, and placenta previa. In the nonhyaline group, one cesarean section was performed for placenta previa. Of the infants with hyaline membranes, most were in poor condition at birth, with diagnoses of atelectasis or intracranial hemorrhage, lived an average of 30 hours, and showed atelectasis or intracranial hemorrhage at autopsy. Those babies without hyaline membranes were in better condition at birth, lived up to 25 days, and less often had pulmonary or brain complications.

Analysis of the deaths of our premature infants in the neonatal period for the weight groups between 1,000 and 2,500 grams over the past five years shows a small decline in deaths from hyaline membrane. Beginning in September, 1950, the oxygen flow in the nursery incubators was decreased from 6 to 1½ L. per minute. With the progressive improvement in pediatric care, it is hazardous to conclude that lowered oxygen concentrations reduced the number of deaths from hyaline membrane. However, clinically, premature infants progressed very well during this period without high oxygen therapy and the over-all premature mortality was reduced (Table I).

TABLE I. NEONATAL DEATHS OF PREMATURE INFANTS ASSOCIATED WITH PULMONARY HYALINE MEMBRANES AT THE COLORADO GENERAL PREMATURE CENTER, JULY 1, 1948, THROUGH JUNE 30, 1953, COMBINED INSIDE AND OUTSIDE SERVICES

YEAR	LIVED	DIED	PER CENT MORTALITY	NO. DIED HYALINE MEMBRANES	RATE OF H.M. DEATHS TO TOTAL ADMISSIONS
1948-1949	177	32	15	12	6%
1949-1950	199	43	18	15	6%
1950-1951	215	35	14	13	5%
1951-1952	218	30	12	13	5%
1952-1953	241	25	9	11	4%

Oxygen in incubators was decreased from 6 to 1½ L. per minute in September, 1950. This report includes infants from 1,000 to 2,500 grams. Autopsy rate varied from 90 to 100 per cent.

Comment

Even though a multitude of animal investigations is not the equivalent of one experiment done on the human being, certain tentative inferences may be made from animal studies concerning physiopathology in man. The difficulty arises as to how many and how big these inferences can be and still remain

plausible. In any event, it is hoped that a few of the cold experimental facts contained herein may find the warmth of, at least, clinical speculation.

Development and Regression of Hyaline Membranes.—

An important aspect of this project centered about the study of experimental hyaline membrane resorption. By exposing guinea pigs to high oxygen for 32 to 64 hours and then sacrificing them at regular intervals, the development and regression of these membranes could be followed. Animals which showed respiratory embarrassment at the conclusion of high oxygen exposure and were returned to room air failed to disclose permanent lung damage.

From histologic examination of experimentally produced hyaline membranes by the hematoxylin-eosin and the Gömöri trichrome stains, the epithelial origin of hyaline membranes could be demonstrated. Progressive stages in the transition of a normal intact epithelium into cellular degeneration and hyaline-like membrane formation were regularly observed. By comparison of the lungs of the experimental animals and the newborn infants, both types of membranes could be localized to the terminal bronchioles and alveolar ducts. Only occasionally was hyaline material found in an expanded or collapsed alveolar sac, and rarely in the large bronchioles. The presence of edema, infection, hemorrhage, foreign material, atelectasis, or even emphysema was often an accidental factor depending upon species difference, degree of pulmonary maturity, and the presence of disease or injury. From histochemical analysis using the Sudan IV, Feulgen, and periodic Schiff reactions, both types of membranes contained fat, carbohydrate, and probably also protein. From careful study of membranes of the newborn and those produced experimentally with high oxygen, it seems reasonable to infer that pulmonary hyaline membranes may be of similar composition though not necessarily of the same etiology; likewise, when premature infants suspected of having hyaline membrane disease live over 4 days, they may resolve the pulmonary damage without sustaining permanent injury.

It seems hardly necessary to point out that a positive fat stain no longer means vernix caseosa; that a positive polysaccharide reaction does not reflect a sugar deposit from diabetic liquor amnii; and that a quasi-positive protein test does not limit the origin of hyaline membranes to the protein of edema or amniotic fluid.

Significance of Atelectasis.—

A very important difference, as emphasized by Arey and Anderson,[14] between the lung of the premature infant and the oxygen-damaged lung is the presence of atelectasis in the newborn. According to Potter,[13] this atelectasis is of the secondary or resorptive type and should be considered a primary cause of death. In this study, no atelectasis could be produced in guinea pigs by exposure to high oxygen. In a recent discussion of the physiopathology of atelectasis, Peck and Levin[12] enumerated the three major requisites for the development of atelectasis: first, a mechanical obstruction; second, sufficient distal circulation to allow gas absorption; and, third, no accessory means for air entry distal to the obstruction. The safeguards of the

normal lung to combat the formation of atelectasis are: an efficient ciliary action from a normal epithelium; a normal exudate from bronchial mucosa; an efficient collateral respiration; an efficient cough mechanism; and an absence of foreign material or inflammation in the bronchi. In the lung of the immature infant, it is obvious that a majority of these safeguards are either underdeveloped or absent. Therefore, atelectasis with or without hyaline membranes is common in the premature infant, whereas, in the experimental animal, full-term infant, or adult human being, these safeguards are functioning well and atelectasis is seldom observed. Whether atelectasis accompanies, initiates, or follows hyaline membrane formation in the premature infant, its unmistakable presence certainly is important. But its mere presence does not necessarily imply a fundamental difference in the pathogenesis of pulmonary hyaline membranes in the experimental animal, the newborn infant, and the adult.

Alteration of Hyaline Membranes by Aerosols.—

Because a major part of the pulmonary pathology of high oxygen poisoning was pulmonary edema and inflammatory reaction, agents useful in reducing surface tension and dissolving secretions were employed in an attempt to alter the clinical course of experimental high oxygen pathology of the lung. On the basis of Joseph Miller's[11] considerable experience in the use of aerosol detergents in pulmonary disease, Duponal C and Alevaire were selected for use in the study of changes in the pulmonary pathology of oxygen poisoning. Duponal C was chosen in a 1 per cent solution because of its known toxicity. This lethal concentration produced marked epitheliolysis and early death of guinea pigs in high oxygen. Alevaire in a 0.1 per cent solution, selected because of its known nontoxicity, not only proved relatively safe but very little hyaline membrane formation could be found in the animals' lungs. Although aerosol detergents do not prevent experimental high oxygen hyaline membrane formation, it is possible that the less toxic ones may prove helpful in the prevention and treatment of hyaline membrane disease in the newborn.

Another "wetting agent" used as an aerosol deserves mention at this time. In Luisada's[10] studies on experimental and clinical acute pulmonary edema, marked improvement occurred with an ethyl alcohol aerosol. Only minor amounts of hyaline membrane and epithelial damage were noticeable in the lungs of animals subjected to continuous 75 per cent ethyl alcohol aerosol. To avoid intoxication and pulmonary irritation, it appears from the work of Lester and Greenberg[9] that a concentration of 7 mg. per liter of inspired air in the human being ought not be exceeded.

Effect of Hormones on High Oxygen Pulmonary Pathology.—

Perhaps the most striking but least understood reaction in this series of high oxygen experiments took place in guinea pigs given various types of hormones. ACTH and high oxygen produced earlier deaths, more epithelial damage, increased lung infection and hyaline membranes. This agrees with Bean's[2] experience of decreased pulmonary pathology in hypophysectomized rats and an increased lung damage with cortisone. It appears that steroid

hormones from the adrenal cortex apparently enhance the toxic action of high oxygen but are not necessary for the initiation of this pathologic process.

In the large controlled series of guinea pigs given estrogen, progesterone, and chorionic gonadotropins, the pulmonary pathology of high oxygen was most rapid and profound. These were the only substances in our experiments which produced a fulminating type of vascular and epithelial damage. Our interest in the role of hormones and high oxygen poisoning had been aroused by Chapple's[14] suggestion of the relationship between hormones and hyaline membrane disease. Karnofsky[7] reported that chorionic gonadotrophin and progesterone had a detrimental effect on rabbits exposed to aerosolized tubercle bacilli while estrogen had a protective influence. Our experiments indicate that both hormones have toxic and lethal actions, especially for the female. Since these massive doses of hormones have no effect on the control animals' lungs, it is likely that they did not directly damage pulmonary

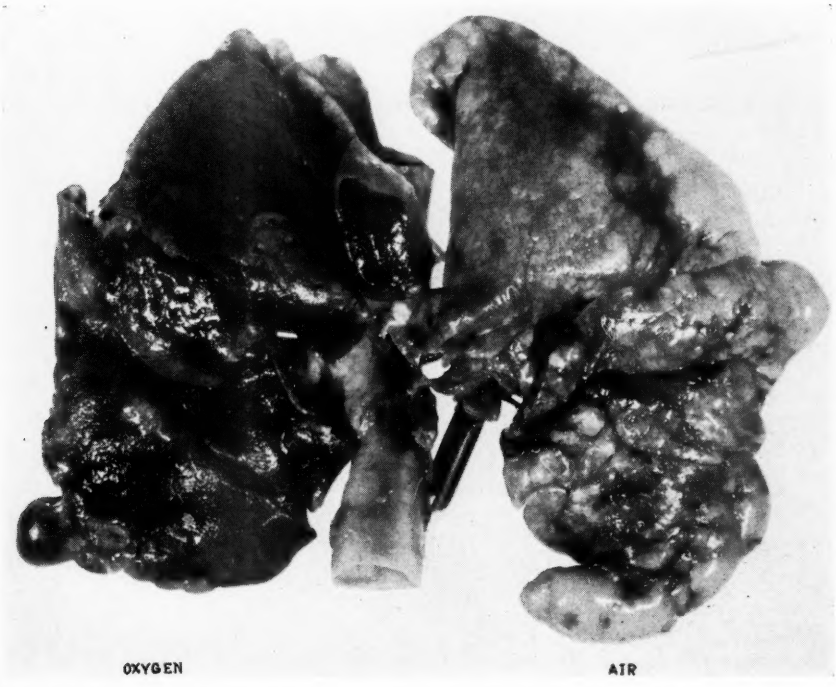

Fig. 5.—Local toxic action of high oxygen. This dog was given 100 per cent oxygen to the left lung and ordinary air to the right and was killed at the end of 7 days. Note the liver-like consolidation of oxygen poisoning in the left lung. (Courtesy Chapin and Hohl, Department of Physiology, University of Colorado, School of Medicine.)

tissue in the doses used. The animals placed in 98 per cent oxygen 25 hours after injection of sex hormones did not develop this fulminating lesion. These animals probably were able to detoxify, metabolize, balance, or excrete these hormones prior to exposure to oxygen poisoning. It is intriguing to theorize that a high level of circulating steroid hormones, which the premature infant cannot "metabolize," exerts the initial adverse effect, perhaps as a surface active agent, upon fragile capillaries mainly at their point of contact with the

external environment, the lungs. Breathing air under such circumstances may be irritating enough to produce pulmonary injury and death. Breathing high oxygen concentrations for long periods may simply enhance the whole deleterious process.

Local Toxicity of High Oxygen.—

In the etiology of oxygen intoxication, high oxygen per se, carbon dioxide, pH, toxins, or almost any disturbed metabolic function has been advanced as a possible cause. In these and most other experiments where animals were exposed to high oxygen at sea level pressure, the primary visible effect was upon the respiratory apparatus. Oxygen behaved as a local irritant to the pulmonary epithelium and lung capillaries. Preliminary experiments by Chapin and Hohl[4] are suggestive of the local toxicity of high oxygen. The right lung of one dog was aerated with oxygen while the left lung of the same animal received air. Fig. 5 shows the marked difference in the two lungs. The side receiving high oxygen showed the usual liverlike consolidation while the one receiving air appeared relatively normal.

Suggested Pathogenesis of Hyaline Membrane Disease

Our explanation for pulmonary hyaline membrane disease and its associated pathology may be outlined as follows: Certain *extrinsic* factors like maternal disease and obstetrical complications may cause the onset of premature labor. A *predisposing* factor of fetal anoxia in pregnancy, labor, or delivery increases capillary fragility. A *precipitating* factor, extrauterine respiration, initiates the bronchiolar and alveolar duct injury with resultant hyaline membrane formation. *Aggravating* factors, principally immaturity but also high oxygen, fetal disease, or injury, and possibly high steroid levels, further enhance pulmonary epithelial and capillary injury.

TABLE II. SUMMARY OF THE EXPERIMENTAL PRODUCTION OF PULMONARY HYALINE MEMBRANES BY EXPOSURE TO 98 PER CENT OXYGEN

NUMBER OF GUINEA PIGS AND TYPE OF EXPERIMENT	PERCENTAGE WITH ONE PLUS OR MORE HYALINE MEMBRANES	DURATION OF LIFE IN HOURS		
		AVE.	MIN.	MAX.
30 normal controls	0	0		
10 oxygen controls	80	49	35	56
10 low humidity	70	72	62	76
10 high humidity	80	73	48	136
10 hyaluronidase (A)*	100	93	63	132
20 trypsin (A)	60	75	62	89
10 Duponal C (A)	60	51	22	74
10 Alevaire (A)	20	87	72	103
10 alcohol (A)	10	69	66	77
10 amniotic fluid (A)	50	67	53	98
10 thromboplastin (A)	40	101	81	130
10 ACTH	70	58	42	68
10 estrogen	50	37	17	56
10 progesterone	0	17	14	20

*(A)—Aerosol.

All animals except normal controls died spontaneously in high oxygen. The normal control animals were killed in air.

Conclusions

1. Hyaline membranes can be produced in 75 per cent of guinea pigs by exposure to 98 per cent oxygen at sea level pressure from 40 to 100 hours.

2. Experimental animals with oxygen-produced hyaline membranes that survive show no evidence of residual lung damage five weeks after exposure.

3. Specific and nonspecific staining reactions are similar in naturally occurring and experimentally produced hyaline membranes. This suggests a similar composition for all pulmonary hyaline membranes without inferring the same etiology for all types.

4. From histologic comparison, pulmonary hyaline membranes in experimental animals and those in the newborn seem to be the result of injury to the alveolar duct and terminal bronchiolar structures.

5. Atelectasis and intracranial hemorrhage were frequently associated with hyaline membrane disease in infants but were not found in animals killed by exposure to high oxygen concentrations.

6. Aerosols of Alevaire and alcohol behaved in a relatively nontoxic fashion and were accompanied by little hyaline membrane formation in experimental animals.

7. Animals given large doses of steroid hormones died rapidly in high oxygen with a fulminating type of pulmonary vascular injury. The possible significance of this finding is discussed.

8. Although high concentrations of oxygen (over 70 per cent at sea level pressure) given continuously and for prolonged periods to animals or human beings are injurious to pulmonary epithelium, certainly they are not the sole cause of hyaline membrane disease in the premature infant. However, high oxygen (over 70 per cent) can be an aggravating factor which may enhance pulmonary damage to the premature infant.

Our gratitude is extended to Mr. Glen R. Mills and his staff for preparing the photomicrographs; to Dr. R. M. Mulligan for his original observations; and to Vera E. Drose for her research assistance.

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Discussion

DR. R. L. NEWMAN, Kansas City, Kan.—Drs. Bruns and Shields have beautifully demonstrated an acceptable method of reproducing hyaline membranes in the lungs of animals. The question still remains as to how they are produced in newborn infants. The authors propose that it is, perhaps, a variable combination of the factors of maternal disease, obstetrical complications, fetal anoxia, extrauterine respiration, immaturity, high oxygen concentration, fetal disease, fetal injury, and high steroid levels. All premature infants certainly are affected by many of these factors and there is no doubt that such infants are very susceptible to the lesion as compared with older infants, children, and adults. Yet hyaline membranes have been found in infants that die within an hour or two after birth, suggesting that such factors as high oxygen levels would have very little time to exert an appreciable effect.

No one, at the present time, has the necessary ability to make a positive diagnosis of pulmonary hyaline membranes in newborn infants without microscopic examination of the lungs. The lesion can only be suspected. However, some infants suspected of having the lesion apparently recover from the hyaline membrane syndrome while continuing to breathe high concentrations of oxygen. If high oxygen concentration per se is a factor in producing hyaline membranes in newborn infants, it will require considerable ingenuity to explain their recovery under those circumstances.

With improved pediatric care there has been improvement in the survival of premature infants over the entire country in the last five years. That fact would seem more logically to account for the improvement in mortality figures presented by the authors rather than to reduction of oxygen concentration administered to such infants.

One cannot refrain from conjecturing upon the percentage of premature infants that would demonstrate the presence of hyaline membranes if all the lungs of such infants could be adequately biopsied. Perhaps, in the authors' words, they are truly "eosinophilic herrings," and it is conceivable that a substantial majority might demonstrate the presence of the lesion in varying degrees.

Dr. Herbert Miller, Professor of Pediatrics at the University of Kansas Medical Center, has established what he believes to be a normal pattern of respiration in newborn infants. When infants establish this pattern within one hour after delivery, they can be expected to survive and develop normally. If this pattern of normal respiration is not established, and it is in this group that pulmonary hyaline membranes are encountered, 25 per cent of the infants will die, and 75 per cent survive, although it is impossible to predict in the individual infant whether survival or death will be the end result.

Various experimental methods and agents have produced pulmonary hyaline membranes in animals. Those include cerebral injury and vagotomy, suggesting a possible neurogenic factor, as well as many types of pulmonary irritants. The results lead to confusion in ascertaining specificity of the lesion as related to any one factor or agent.

The use of 75 per cent ethyl alcohol aerosol as a therapeutic agent in this lesion demonstrated interesting experimental results. Perhaps it is unfortunate that adults are not more susceptible to the lesion since the use of such an agent could become rather popular, at least with certain individuals, and a considerable amount of physical effort would be avoided.

It is impossible to contest the facts as presented. The interpretation of those facts as related to clinical medicine is subject to some variation and disagreement.

TOXEMIA OF PREGNANCY—ACTH AND CORTISONE THERAPY*

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CONCEPTS regarding toxemia of pregnancy, the disease of theories, have been further complicated with the advent of ACTH and cortisone. Fragmentary evidence of the pharmacologic activity of these hormones in pregnancy has led to opposed theories of etiology and treatment of toxemia of pregnancy. Some have reasoned that the administration of cortisone would exert beneficial effects.[1-5] Others have suggested that a disturbance in the adrenocortical steroid metabolism in pregnancy played an important role in the etiology of this disease.[1, 2, 6, 7] Practical experience with the administration of ACTH and/or cortisone during pregnancy has not been sufficiently extensive for accurate evaluation.[3-5, 8-15]

This report deals with observations upon 24 obstetricial patients who received ACTH and/or cortisone for a sufficient period and in sufficient dosage to permit clinical evaluation. Nine patients, suffering from toxemia of pregnancy, received either ACTH and/or cortisone as part of their treatment.

Materials and Methods

The following ACTH preparations† were used: (1) short-acting aqueous ACTH; (2) ACTH dissolved in a depot substance (Adactar 32); (3) Acthar Gel; (4) oxycellulose-purified ACTH; and (5) ACTH in polyvinyl pyrrolidone. ACTH was given intramuscularly, either in divided doses of 20 to 25 units, totaling 120 units daily, or by single injections of depot substances of 80 to 100 units daily. When administered intravenously, 20 to 25 units of ACTH was dissolved in 500 c.c. of 5 per cent glucose in water and infused slowly over a period of 6 to 8 hours. Cortisone was used as cortisone acetate, orally or intramuscularly, in amounts varying from 12.5 to 300 mg. daily.

Clinical Material

The clinical material has been analyzed for possible solution to the following questions:

1. Are ACTH and/or cortisone of value to the patient suffering from toxemia of pregnancy?

2. Do these hormones favor the development of toxemia of pregnancy?

3. What pharmacological effects are evident in pregnancy from administration of either ACTH or cortisone in doses generally used in clinical practice?

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*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston Texas, Nov. 5, 6, and 7, 1953.

†The short-acting aqueous ACTH, the oxycellulose-purified ACTH, and ACTH in polyvinyl pyrrolidone were supplied through the courtesy of Parke, Davis & Company of Detroit, Mich.

Adactar 32 and Acthar Gel were obtained through the courtesy of Armour Company of Chicago, Ill.

TABLE I.—CASE 2, H. J.

DATE	9/17	9/18	9/19	9/20	9/21	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30
Eosinophil count		38	0	—	—	0	0	—	85	106	—	160		
Serum Na, meq./L.		140	137	133	129	135	135	142	135	—	135	135	135	
K, meq./L.		5.0	4.2		4.0	4.1	3.9	3.5	3.8	—	4.1	4.1	4.4	
Cl, meq./L.		103	107	107	108	—	—	110	—	94	94	92	92	
Uric acid, mg. %	4.1	5.7	8.0	4.2	4.9	5.1	5.2	4.6	5.2	—	4	4	3.5	
Sugar, mg. %	80	75	90	129	113	109	85	—	85	—	92	109	100	
NPN, mg. %	23	28	37	48	—	—	—	—	—	—	—	—	—	
24 hour urine														
Na, Gm.	.258	1.52	—	.670	.680	.128	.610	—	—	2.30		1.70	2.50	
K, Gm.	1.72	1.92	—	1.90	2.20	2.30	1.60	—	—	1.40		.840	1.80	
Alb., Gm.	.360		.430	.200	.520	.750	—	—	—	1000	—	.600	.600	
Vol., c.c.	400	470		500	650	630	470			1350		560	860	
Qualitative albuminuria	2+	1+	2+	1+	1+	2+	1+	1+	1+	3+	2+	1+	1+	1+
BP, mm. Hg	174/90	162/90	160/80	160/80	170/80	145/80	158/80	198/90	180/110	170/100	160/100	140/90	120/80	130/80
Weight (pounds)	151	147	143	142	142	140	141	—	131	129		124	121	119
Medication, ACTH		100	100	100	100	75	50	D*						

*D, day of delivery.

1. Toxemia of Pregnancy, Possible Benefit From ACTH or Cortisone

Nine patients suffering from toxemia of pregnancy were treated with ACTH and/or cortisone. These cases are summarized as follows:

ACTH Group.—

CASE 1.—M. B., aged 40 years, para ii, gravida iii, was admitted for treatment of toxemia of pregnancy in the thirty-sixth week of gestation. Her blood pressure was 150/100, one plus albumin was present in the urine, and she demonstrated one plus ankle edema.

Treatment consisted of bed rest, mild sedation, and administration of ACTH, 25 units in 10 divided doses over an interval of three days—total dose 250 units.

Under therapy the blood pressure decreased to 118/70. The qualitative test for albuminuria became negative and she lost 2½ pounds.

She was readmitted to the hospital at term and was delivered of a normal male infant who weighed 3,230 grams. The blood pressure was 126/80 at the time of delivery.

CASE 2.—H. J., a primigravida, aged 41 years, developed signs of toxemia in the thirty-first week of gestation. The diagnosis was based upon a weight gain of 14 pounds in three weeks, elevation of blood pressure from 120/72 to 180/90, the development of pretibial edema, and two plus albuminuria.

Treatment consisted of bed rest, mild sedation, restriction of sodium chloride intake, limitation of fluids, and dehydrating measures. ACTH, 100 units for 4 days, 75 units for 1 day, and 50 units for 1 day, was administered. The total dose administered was 525 units.

The results of therapy are detailed in Table I.

At 33 weeks' gestation the membranes ruptured spontaneously and after 5 hours of labor the patient delivered a living, active premature male infant that survived.

CASE 3.—L. D. was a 32-year-old white gravida ii, para i. Her prenatal course was uneventful until 36 weeks' gestation when she gained 11 pounds in an interval of 2 weeks. Her blood pressure was elevated to 142/90, urine was negative for albumin, and pretibial edema was four plus.

Treatment consisted of bed rest, restricted sodium chloride diet, the administration of ammonium chloride, 4 grams daily, and minimal sedation. ACTH administration, 30 units every 6 hours, was continued for 6 days. The total dose was 720 units.

Under treatment the weight declined from 164 to 156 pounds, the blood pressure from 142/90 to 120/80, and the pretibial edema disappeared.

She was readmitted two weeks after treatment in labor and was delivered of a normal full-term male infant. Blood pressure at the time of her second admission was 150/100. Table II gives the details of her blood chemistry while on therapy.

TABLE II. BLOOD CHEMISTRY OF CASE 3, L. D.

DATE	8/27	8/28	8/29	8/30	8/31	9/1	9/2
Uric acid, mg. %	4.5	4.4	4.7	4.0	4.7	4.4	5.6
Plasma Na, meq./L.		138	136	137	136	136	136
Plasma K, meq./L.		4.2	4.2	4.7	4.4	4	4.7
Plasma Cl, meq./L.		100	94	102	104	100	104
Eosinophile count per c. mm.		16	6	0	0	0	10
Blood sugar, mg. %		87	107	92	100	85	80

Cortisone Group.—

CASE 4.—A. S., white, aged 36 years, was admitted for treatment of toxemia which developed in the thirtieth week of gestation. Initial studies showed the blood pressure to be 230/130, albuminuria four plus, with extensive ankle edema.

TABLE III. CASE 5, S. DEY.

DATE	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/1	10/2	10/3	10/4
								D*					
Eosinophil count				139	16	—	3	—	—	3	37	—	
Serum Na, meq./L.		136	136	142	135	132	132	138	137	137	127		
K, meq./L.		4.3	4.1	3.5	3.7	4.6	4.5	4.4	4.0	4.3	4.5		
Cl, meq./L.		116	103	93	101	105	106	96	98	97	110		
Uric acid, mg. %		4.2	3.8	3.6	4.4	3.6	3.5	3.3	4.4	4.3	3.6		
NPN, mg. %		31	22	31	30	35	37	33	29	33	31		
Vol., c.c.		480	1620	790	1045	1080	560	1125		560			
24 hour urine													
Na, Gm.		.964	3.01	1.52	.627	.324	.114	.358		.940			
K, Gm.		.586	2.90	1.06	1.20	2.30	2.00	3.30		1.22			
Alb., Gm.		.500	1.20	2.70	.850	1.30	—	2.20		.480			
Qualitative albuminuria		4+	3+	2+	3+	2+	2+	2+	2+	2+	2+	3+	
BP	200/100	160/100	170/100	170/100	150/100	150/100	160/100	170/100	190/120	150/100	140/110	130/100	
Weight (pounds)		—	130	128	128	128	128½	129½	119½	117½	115	113	
Cortisone					300 mg.	300	300						

*D, day of delivery.

Treatment consisting of bed rest, mild phenobarbital sedation, and restriction of fluids and sodium chloride resulted in little improvement after two days. Cortisone therapy consisted of 200 mg. for 5 days, 100 mg. for 8 days. The total amount of cortisone administered over a period of 13 days was 1,800 mg. Her blood pressure when cortisone therapy was instituted was 170/135. When cortisone therapy was terminated, the blood pressure was 160/110, and there was one plus albuminuria.

Delivery followed amniotomy and Pitocin induction. The surviving male infant appeared normal.

CASE 5.—S. deY. The pregnancy of this 25-year-old gravida i, para 0, was uneventful until the thirty-seventh week. Because of mild symptoms of toxemia, she was placed on bed rest, low sodium chloride diet, phenobarbital and ammonium chloride. One week later her blood pressure was 182/100 and the urine tested four plus for albumin.

Cortisone was administered intramuscularly, 100 mg. 3 times daily for 3 days.

Other than a feeling of well-being, there was little evidence of clinical improvement.

Labor began spontaneously after 3 days of cortisone therapy, resulting in delivery of a normal male infant (Table III).

CASE 6.—J. R., aged 29 years, Negro, para 0, gravida i, was admitted for treatment of toxemia in the thirty-second week of gestation. During the week prior to admission her weight increased by 8 pounds and she complained of headache and dyspnea.

Upon admission, the blood pressure was 170/110, the urine showed four plus albumin, and periorbital and pretibial edema was evident.

For 8 days a conservative bed rest program was followed. In the next 7 days she received 18 injections of cortisone acetate, 100 mg. each, a total of 1,800 mg.

During the period when her treatment consisted of bed rest, mild sedation, ammonium chloride, and limitation of sodium chloride and fluids, her blood pressure decreased to 145/105. The urine was consistently positive for albumin. Under the cortisone regime, the blood pressure fell to 130/90 and albuminuria persisted. Labor was induced and the delivery was uneventful. The female infant survived.

CASE 7.—S. B., a 22-year-old, gravida ii, para 0, was admitted at term having convulsions. No details of her prenatal care were available from her physician although there was the impression that her weight gain had been excessive.

Following her first convulsion, her blood pressure was 150/115. The urine contained four plus albumin and showed granular casts.

Funduscopic examination showed retinal arterial spasm, punctate hemorrhage, and papilledema.

Convulsions were controlled with morphine sulfate and 50 per cent magnesium sulfate given intramuscularly. Cortisone acetate, 50 mg., was given intramuscularly and repeated every 6 hours for 3 days, then every 12 hours for 2 days. The total dose was 800 mg.

No further convulsions occurred and the blood pressure stabilized at 140/100. Daily urinary loss of albumin remained constant at about 6 Gm. each day. Labor followed amniotomy and Pitocin induction. Uneventful delivery of a living normal 3,390 gram female infant resulted.

CASE 8.—E. C., aged 23 years, white, gravida i, para 0, developed elevation of blood pressure, albuminuria, and pretibial edema in the thirty-ninth week of twin gestation. Upon admission to the hospital, examination disclosed: blood pressure 158/90; hyperreflexia, two plus pretibial edema, and two plus albuminuria. In addition to bed rest, dehydration, restriction of fluids and sodium chloride, cortisone acetate, 50 mg., was administered every 4 hours for 8 doses, then every 6 hours for 4 doses. The total dose was 600 mg.

When she was under cortisone therapy, the blood pressure fell to 116/76. Following discontinuance of cortisone and relaxation of the strictness of the conservative program, the blood pressure rose to 170/100. Her weight had diminished from 160 to 150½ pounds. Albuminuria remained unchanged.

Delivery of living twins followed induction of labor. Neither infant demonstrated evidence of adrenocortical insufficiency.

CASE 9.—H. DisB. (This case is included through the courtesy of her obstetrician, Dr. Tennyson Williams of Delaware, Ohio.) This 29-year-old, para i, gravida ii, had been under treatment with cortisone, 40 mg. daily, for over two years because of intractable asthma and eczema. While under this cortisone program, she conceived and the anticipated date of confinement was Feb. 24, 1953. In December of 1952, the diagnosis of twins was established. In consultation with Dr. Williams, it was suggested that ACTH be substituted for cortisone. This was accomplished during the month of January, 1953. At the time of delivery, she was receiving 50 units ACTH daily with fair control of the asthma and eczema.

Living twins in excellent condition were delivered Jan. 31, 1953, after spontaneous rupture of the membranes. Because of respiratory distress ACTH was increased to 75 units on the day of delivery and continued post partum.

The prenatal course revealed consistently normal blood pressure and urinary findings. On the fourth postpartum day, elevation of the blood pressure was first recorded. The patient had several convulsions on the fifth postpartum day. Her blood pressure after the first convulsion was 160/90. The urine was positive for albumin.

ACTH was reduced to 25 units daily. Subsequent to reduction of ACTH, disturbing asthma symptoms recurred. ACTH was gradually increased to control these symptoms until 75 units daily was reached 5 days after the convulsive episode. Although no further convulsions occurred, the blood pressure showed a tendency to rise and was recorded as 180/90. ACTH was reduced to 50 units and the blood pressure gradually fell to the prepregnancy level.

Comment.—

Analysis of these cases supplies little evidence that ACTH and/or cortisone is of benefit to patients suffering from toxemia of pregnancy. Any improvement noted in the study was hardly more than could be expected from the usual toxemia program used in this hospital. This program consists of bed rest, mild phenobarbital sedation, and limitation of the intake of sodium chloride and fluids. When edema is a prominent feature, elimination of fluids is encouraged through the administration of magnesium sulfate by mouth. In this study for the evaluation of the effectiveness of ACTH and/or cortisone, the administration of these hormones was superimposed upon the usual toxemia program. Except for a sense of well-being, no benefit was evident from the administration of ACTH and/or cortisone in patients suffering from varying degrees of toxemia of pregnancy. Conversely, no detrimental effects were observed. The outstanding example of this was the patient with active eclampsia, S. B., of Group 1. She received cortisone in addition to the usual treatment for eclampsia. No further convulsions occurred during cortisone therapy.

2. Do ACTH and/or Cortisone Favor the Development of Toxemia of Pregnancy?

Sixteen patients received either ACTH and/or cortisone during a period of 3 weeks and/or a total dosage of at least 1,000 mg. They served to evaluate the theory that these hormones favor the development of toxemia of pregnancy. In this group of patients, treatment was administered for some condition not related to pregnancy.

Criteria accepted in this study for the diagnosis of toxemia of pregnancy were as follows: Elevation of systolic blood pressure of over 30 mm. Hg, and diastolic blood pressure of over 20 mm. Hg, above the patient's usual blood pressure, the development of albuminuria, and a weight gain of over 8 pounds in a 4 week interval. The results of this study are recorded in Table IV.

TABLE IV. BLOOD PRESSURE

PATIENT	HORMONE	DURATION		AMOUNT	MAXIMUM WHILE UNDER TREATMENT	AT TERM	WEIGHT GAIN	ALBUMIN	EDEMA
		MONTHS	DAYS	(NEG.)					
H. D.	ACTH	3	22	8,350	130/72	120/80	32	0	0
B. W.	ACTH	3d		300					
	Cortisone	4	½	6,500	130/80	146/90	23	0	0
L. F.	ACTH	4		6,405					
	Cortisone		3	300	124/84	144/77	21½	0	+
M. R.	ACTH	6	⅓	6,365	120/80	100/80	24	0	+
L. P.	Cortisone	9+		5,010	110/70	128/82	23¾	0	0
M. L.	ACTH	3	18	4,480	130/70	124/70	13	0	0
N. H.	ACTH	3		3,130	130/70	110/60	23	0	0
D. W.	ACTH	3	½	2,520	126/78	128/78	13	0	0
D. M.	ACTH	1	5	1,520	112/65	120/80	18	0	0
D. M. (2)	ACTH	3	11	3,640	138/86	120/80	0	0	0
S. B.	ACTH	2	⅓	1,400	120/68	114/80	18	0	0
D. M. (1)	ACTH		18	1,060	120/80	115/80	23	0	0
L. L.	ACTH	2		1,000	130/80	118/68	30	0	+
F. F.	ACTH	2	22	4,000	138/74	110/62	15	0	+
H. D.	Cortisone	8		8,180					
	ACTH	1		1,325	148/82	120/80	42 (twins)	0	0
M. P.	ACTH	1	4	1,560	128/80	120/70	13¼	0	0

The highest blood pressure recorded was 148/82. This was an isolated unsustained reading. The maximum elevation in blood pressure, except for the one cited above, was 28 mm. Hg systolic and 15 mm. Hg diastolic. Albuminuria did not develop in any patient while under therapy.

Transient excessive weight gains were occasionally observed. Restriction of sodium chloride promptly controlled this feature. The greatest weight gain recorded, except for a patient with twins, was 32 pounds. This occurred in a patient who received 8,350 mg. cortisone over a period of 112 days.

One patient in this group had suffered from toxemia of pregnancy during a previous pregnancy. Administration of ACTH, 6,405 units, over a period of 120 days did not cause recurrence.

However, Case 9, H. DisB., reported in the toxemia group, deserves special consideration in this respect. She developed postpartum toxemia while receiving 75 units ACTH daily for intractable asthma and eczema. Active measures to control the convulsions resulted in amelioration of symptoms. ACTH was continued in reduced dosage during this period. As the patient improved, restrictions were relaxed and ACTH was increased under the demands of the severity of the asthma. Hypertension recurred after 7 days. The relationships of ACTH to these postpartum episodes are speculative.

Pharmacological Effects of ACTH and/or Cortisone in Pregnancy

The pharmacological effects of ACTH and/or cortisone during pregnancy were studied through determination of blood electrolytes, sugar, and uric acid.

Plasma Potassium.—

Seventy-five determinations on 19 patients were made for plasma potassium. The highest value obtained was 23.1 mg. per cent (5.9 meq./L.) and the lowest 11.3 mg. per cent (2.9 meq./L.). The average was 16.2 mg. per cent (4.2 meq./L.). No electrocardiographic evidence of potassium imbalance was observed.

Plasma Sodium.—

Seventy-one determinations for plasma sodium were performed on 19 patients. These averaged 316 mg. per cent (137 meq./L.). The highest was 324 mg. per cent (141 meq./L.) and the lowest was 285 mg. per cent (124 meq./L.).

Plasma Chlorides.—

Sixty-seven determinations were done on 19 patients with the following results: Average 600 mg. per cent (103 meq./L.), lowest 510 mg. per cent (87.5 meq./L.) and highest 685 mg. per cent (117 meq./L.).

Normal values for these electrolytes in this laboratory are: Potassium 18 to 22 mg. per cent (4.6 to 5.6 meq./L.), chlorides 550 to 620 mg. per cent (94 to 106 meq./L.), and sodium, 310 to 340 mg. per cent (135 to 148 meq./L.).

Blood Sugar.—

Seventy blood sugar determinations were performed on 20 patients. These ranged from 129 to 45 mg. per cent. The average was 90 mg. per cent. Failure of these patients to develop hyperglycemia was an unexpected observation. One patient on two occasions, while under ACTH therapy, developed hypoglycemia with blood sugar values of 45 mg. per cent.

Uric Acid.—

Blood uric acid values were not consistently obtained. In several patients suffering from toxemia of pregnancy, frequent determinations were performed. Although the blood uric acid values were slightly elevated prior to initiation of therapy because of the toxemia, no additional elevation was evident as the result of therapy.

The following 2 patients, D. M. and F. F., treated for 101 and 82 days, and receiving 3,640 and 4,000 units of ACTH, respectively, had frequent electrolyte determinations and are considered representative. They are therefore presented in some detail.

D. M., aged 32 years, gravida iv, para iv, had been given ACTH during her previous pregnancy in the hope of preventing erythroblastosis fetalis. That pregnancy terminated in the birth of a mildly erythroblastotic infant. During the present pregnancy she received a total of 3,640 units of ACTH over a period of 101 days. This pregnancy terminated at 7 months with the delivery of a stillborn erythroblastotic infant (Table V).

F. F., aged 28 years, gravida iv, para ii, received a total of 4,000 units of ACTH in 82 days, in the hope of preventing erythroblastosis. She delivered a normal term infant (Table VI).

TABLE V. D. M.

DATE	2/27	4/25	5/2	5/16	5/23	6/11	6/20	6/27	7/7	7/18	7/25	8/15	8/22	8/29
												D*		
Plasma Na, meq./L.	138	130	136	132	135	136	137	135	136	133	138	137	136	137
Plasma K, meq./L.	4.5	3.7	3.7	5.1	3.7	4.2	3.4	4.6	4.2	4.4	4.6	4.7	4.2	4.9
Plasma Cl, meq./L.	102	108		100	115	105	112	108	112	97	100	95	97	88
Eosinophil count per c. mm.	42	0	2	0	3	40	—	—	0	2	0	—	32	93
Blood sugar, mg. %		72	94	74	97	78	87	82	82	106	109	85	94	103
Uric acid, mg. %								3.1		3.1		4.0	—	4.0

*D, day of delivery.

TABLE VI. F. F.

DATE	2/19	3/4	3/20	3/24	4/4	4/11	4/18	4/28	5/11	5/13	6/15
									D*		
Plasma Na, meq./L.	132	131	132	132	134	131	132	131	130	131	130
Plasma K, meq./L.	4.9	3.9	3.7	3.7	3.7	3.9	3.2	5.6	3.4	4.6	5.1
Plasma Cl, meq./L.	100	92	107	107	108	109	94	108	93		
Eosinophil count per c. mm.	0	34	101	40	13	6		26	86	86	107
Blood sugar, mg. %	85	100	45	45	89		92				100

*D, day of delivery.

Comment.—

The similarity between the symptoms of toxemia of pregnancy and the physiological effects of ACTH and/or cortisone are striking.[6, 7, 16] In nonpregnancy ACTH and/or cortisone can be expected to produce sodium retention, potassium excretion, elevated blood uric acid, increased excretion of 17-ketosteroids, and occasionally albuminuria and hyperglycemia. Also, hypertension, sudden weight gain, and edema are frequently observed. A shift of fluid from the extracellular to the intracellular compartment may occur.[17] Many of these changes occur in toxemia of pregnancy.

The relationship of adrenocorticosteroid metabolism to normal and toxemic pregnancies has recently been studied by Lloyd and associates.[18, 19] They observed increased excretion of poorly water-soluble corticoids in the urine of patients suffering from toxemia of pregnancy. Working with animals, Loeb and collaborators[20] and Masson and Corcoran[21] reported the development of a toxemia-like condition by the administration DOCA and a high-salt diet. Experiments in human beings with healthy adrenal glands did not yield similar results.[22] It has been suggested that eclampsia belongs to the diseases of adaptation.[6, 7, 16] The use of ACTH and cortisone for the treatment of toxemia of pregnancy has been reported by several investigators.

The results of this study were in agreement that the course of toxemia of pregnancy was not significantly altered by the administration of these hor-

mones. On the other hand, neither was there any evidence that ACTH and/or cortisone favored the onset of toxemia. The normal prenatal course of 16 patients who received these hormones for 3 weeks or more and/or in dosages of at least 1,000 mg. showed no tendency toward the development of symptoms resembling those commonly associated with toxemia of pregnancy.

One of the most striking observations was the increased tolerance of pregnant patients to the administration of ACTH and cortisone. This reaction was also observed by Ferguson[11] with ACTH, and by Margulis and Hodgkinson[12] with both ACTH and cortisone. In this respect the reaction of the pregnant woman to ACTH and cortisone is similar to that observed with the administration of stilbestrol[23] and DOCA.[24, 25] Whether this increased tolerance in pregnancy is due to: (1) the tremendous increase in endogenous corticoids,[26] rendering the usual dosage used in clinical practice insignificant; (2) decrease in end organ responsiveness; (3) production or storage of ACTH or corticoids by the placenta; or (4) the production of a physiological antagonist, are problems which must remain speculative for the present.

Conclusions

1. Twenty-four obstetrical patients received ACTH and/or cortisone during pregnancy. Nine patients suffering from toxemia of pregnancy received these hormones as part of their treatment. Fifteen patients received treatment during pregnancy for conditions not related to their pregnancy.

2. ACTH and/or cortisone demonstrated no favorable influence upon toxemia.

3. The administration of ACTH and/or cortisone did not produce symptoms of toxemia.

4. These observations confirmed the impression that pregnant patients demonstrate an increased tolerance to ACTH and/or cortisone.

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Discussion

JAMES HENRY FERGUSON, M.D., New Orleans, La.—I wish to compliment Dr. Hodgkinson and his associates on this clean-cut clinical experiment. Here we have something on ACTH and cortisone that is not an hypothesizing but a stating of facts. We probably all believe that the pituitary and the adrenal cortex have new or altered activities in pregnancy and in pre-eclampsia. Some writers, not always fortified by experience with the medicines but certainly by a series of non sequiturs, have decided that pregnancy toxemia is a state of abnormal quantities of ACTH or cortisone, either too much or too little. Dr. Hodgkinson's work suggests that the problem may not be that simple.

Many of the patients with pre-eclampsia reported in this paper improved while receiving ACTH or cortisone. Some enthusiasts might have claimed success for these hormones. Today's essayist, with admirable restraint, recognizes that the adjunctive treatment he used has been known to improve women with pre-eclampsia.

Hodgkinson's results were the same as in my experiment with ACTH. He treated more patients and used larger doses. The most consistent result that I was able to produce in my patients was heartburn. In 1950 ACTH was more expensive, and as there were cheaper ways of producing heartburn I became discouraged and stopped after treating nine women. I found that the pituitary adrenocorticotropic hormone (ACTH) did not cause or ameliorate pre-eclampsia. Blood glucose, chlorides, protein, and uric acid levels were not influenced. Doses of ACTH that were effective against responsive diseases and could produce some fairly consistent physiological alterations, were peculiarly inert in pregnancy.

I am indebted to Dr. Isadore Dyer for some unpublished data on Rh-sensitized women who were treated with cortisone. He and his co-workers at Tulane have treated over 50 women with an average daily dose of 100 mg. of cortisone. This has been given from the twenty-eighth week of pregnancy until delivery. The patients were seen weekly. A number of biochemical measurements were repeatedly made. It will be sufficient to say at this time that none of the tests was materially altered by the cortisone. He does not believe cortisone caused pre-eclampsia. As would be expected in any group of this size of pregnant women, a few showed excessive water retention. When this happened the drug was reduced and a low-salt diet prescribed. They improved and returned to taking cortisone.

It is true, as Dr. Hodgkinson says in closing, that a number of questions about ACTH and cortisone in pregnancy are yet to be answered. Today I think he has settled with some finality the first questions that would be asked of these drugs: In the usual doses do they help pre-eclampsia? and, Do they make it worse?

DR. EDWIN J. DeCOSTA, Chicago, Ill.—Moore and his co-workers were the first to report on the use of adrenal cortical hormones in the treatment of toxemia. They

presented six patients with severe pre-eclampsia before the Royal Academy of Medicine in Ireland in 1950. In these six patients there was no significant alteration in the blood pressure or albuminuria during treatment and one patient had convulsions while in labor. However, because the patients felt better, their headaches and eye symptoms improved, and urinary output increased, there was the implication that cortisone was of clinical value. At that time it was not well known that cortisone induces euphoria. We now know that one of the best methods of making a dying patient happy is to give him cortisone.

Today we have, I hope, heard the final answer to the enthusiastic implications of Moore, namely, that neither cortisone nor ACTH favorably influences the course of toxemia. Moore used cortisone, the authors used both ACTH and cortisone. Although the effects of ACTH and cortisone might not be identical, the observed results were actually quite similar.

The authors have left themselves open to some criticism. They used five different ACTH preparations, sometimes with, sometimes without cortisone, in varying doses and over various periods of time. Perhaps their results would have been different if they had concentrated their efforts and had minimized the variables. Even though the adrenal hormones, as it turned out, were ineffectual in influencing the course of toxemia, it would have been desirable either to have stabilized the toxemic patients by routine care before the administration of the hormones, or to have given the hormones without complicating the picture by ancillary therapy.

I am in full accord with their conclusions. My own experience is similar: neither ACTH nor cortisone has any demonstrable effect on either the production or amelioration of the symptoms of toxemia of pregnancy. However, on at least one occasion I have witnessed the development of toxemia while a patient was receiving cortisone. This was a pregnant, sensitized, Rh-negative patient who had delivered one severely erythroblastotic child. In a fruitless attempt to save the fetus, we gave this patient 100 mg. of cortisone daily from the twenty-sixth to the thirty-sixth week of gestation. During the thirty-fifth and thirty-sixth weeks she gained 14 pounds while on a salt-poor diet, developed proteinuria, and showed a rise of 40 mm. in the systolic blood pressure. Following delivery of a classical hydropic fetus, the pressure fell to normal and the albuminuria and edema rapidly subsided. During this period she was still on cortisone in decreasing doses.

From the accumulated evidence, it appears that we must look to other than the known hormones of the adrenal gland as a factor in the etiology of toxemia.

I would like to introduce a note of caution. Neither cortisone nor ACTH is an innocuous preparation. Among other effects, there is a suppression of the endogenous production of ACTH. Although the pregnant patient does seem to be very tolerant of these hormones, there is a possibility that exogenous administration may depress normal function sufficiently to interfere with adequate adrenal response to stress. This has been observed in nonpregnant patients with fatal outcome. To minimize this possibility, whenever ACTH or cortisone is used, it seems desirable to continue therapy until after delivery and then to reduce the dose gradually over a period of about two weeks.

DR. MARGULIS (Closing).—I would like to enlarge upon Dr. DeCosta's remark as to the potential danger of giving ACTH and cortisone for a period of hypopituitarism or hypofunction of the pituitary.

This is of special importance to the baby you will deliver. If you give cortisone for a prolonged period of time, there is at least a theoretical possibility, which Dr. Hodgkinson, Dr. Lattinger, and I observed, that the baby might develop immediately post partum a hypoadrenalism which is most likely due to a suppressed pituitary.

With ACTH I do not think the possibility is as great as it is with cortisone, and therefore a switch at the last moment to ACTH would probably, from a theoretical standpoint, be desirable, since ACTH, when tagged, was found to be transmitted to the fetal adrenal cortex.

THE POSTPARTUM BLADDER*

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(From the Departments of Obstetrics and Gynecology and Urology, the Presbyterian Hospital and the University of Illinois College of Medicine, Rush Faculty)

THE effects of pregnancy, labor, and delivery on the urinary bladder and the resultant variations in the cystoscopic picture of the interior of the bladder immediately post partum are often described in obstetrical textbooks and in the medical literature. However, in a careful review, we were unable to unearth authenticated studies with photographs or drawings depicting the condition of the bladder mucosa at this specific time. Because of the apparent hiatus in our obstetrical knowledge it was decided to make a study of a series of patients delivered at the Presbyterian Hospital of Chicago, performing cystoscopic examination immediately following parturition in order to determine the changes that take place in the vesical mucosa as a result of pregnancy, labor, and delivery.

The two generally used encyclopedic obstetrical textbooks[1, 2] carry very brief descriptions, only partially accurate, of the changes produced by labor in the urinary bladder, without substantiating references. There are no allusions to the effects that varying circumstances might have upon the intravesical picture. Bennetts and Judd[3] have come nearest to carrying out a study such as we have made, but the cystoscopies in their series of patients were done 36 to 72 hours after delivery, while ours were made immediately after the completion of labor. Our findings do not coincide with those noted by these authors and we ascribe these discrepancies to the relative lateness in the puerperium at which they carried out their examinations.

Method

At the Presbyterian Hospital of Chicago, most patients are delivered under general anesthesia, using ethylene-oxygen. The majority of patients, excepting grand multiparas, have episiotomy. After completion of the third stage of labor, the episiotomy is repaired and all lacerations are sutured. The anesthesia is then continued and the cystoscopic examination is conducted. No special medications are used before or after the study of the bladder is made, and we have found no postpartum difficulties of any sort that might be attributed to the cystoscopy.

Results

We are herewith reporting on the cystoscopic examination of 71 patients following term delivery. There were 28 primiparas and 43 multiparas in this

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group. The length of labor showed a great variation because the three patients in whom elective repeat cesarean section was done had no labor, the others had labor varying from 48 minutes to 53 hours and 25 minutes. Fifty-four of these women delivered spontaneously while 13 were delivered by forceps, 10 low or outlet and 3 midforceps. Most of the patients in this series had episiotomy. One patient had a breech delivery. The weights of the infants varied from 5 pounds to 10 pounds, 1 ounce.

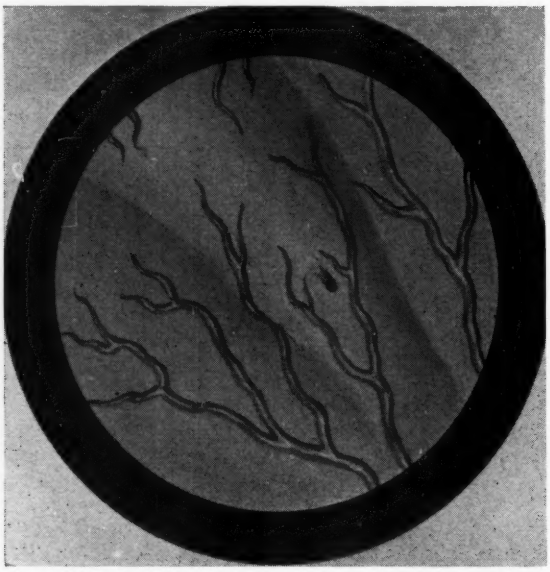

Fig. 1 (Groups 1 and 2).—Postpartum bladder showing hyperemia and engorgement of vessels and deeper hue of mucosa with relatively normal ureteral area.

The postpartum bladder presents a variable picture as seen through the cystoscope. Many factors contribute to these variations but, as would logically be expected, the longer the labor with the fetal head in the maternal pelvis, the greater is the evidence of vesical trauma. Conversely, the shorter the labor the less is the effect upon the bladder mucosa. Some of the elements which would act to increase the damage to the bladder are the difficult midforceps delivery with forceps rotation, the large baby with wide shoulder span, producing difficulty in bringing this diameter through the pelvis, and the stubborn breech extraction. No single bladder picture can be described as a norm for the postpartum patient since the numerous variations seen depend upon the severity and force of the trauma. We feel, though, that we can set up five general groups for purposes of classification:

1. In this group we place the elective cesarean sections in which the picture is essentially that described by McCrea[4] as being typical of the normal bladder during pregnancy. This author says, "The bladder, during pregnancy, shows nothing unusual except vascular engorgement. The mucosa is of a deeper color than normally seen in the non-pregnant woman, as all types of blood vessels are dilated." Added to this we find there is usually an increased amount of edema

and some traumatic mucosal hemorrhage high on the posterior wall where separation from the uterus had been accomplished during the course of the low cervical type of operation (Fig. 1).

2. This group is made up of those cases which would fall into the general classification of precipitate labor. In spite of the fact that these patients present little general evidence of having had a baby pass through the birth canal, there were sufficient intravesical changes to induce us to place them in a classification separate from that of those women who had had elective cesarean section. These changes were indicated by an increase in hyperemia in the region of the bladder neck and trigone with slight-to-moderate increase in edema of these areas. In some instances there are seen a few minute submucosal petechial hemorrhages (Fig. 2).

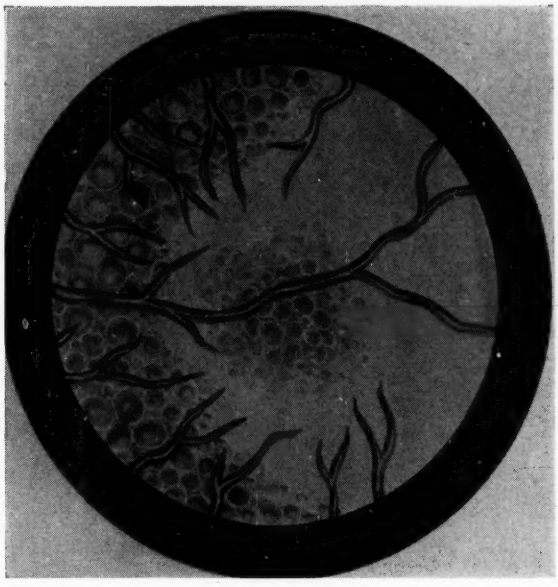

Fig. 2 (Group 2).—Increase in edema, hyperemia, and engorgement of blood vessels.

3. In this group we have placed the average multipara and the unusual primipara in whom the head does not engage much before the beginning of a short second stage of labor. There is, in these patients, additional evidence of trauma to the portions of the bladder that are most affected by the increased contact with the descending fetal head. This consists of the universal occurrence of submucosal petechial hemorrhages of moderate number and degree, and a more marked amount of edema and hyperemia than was observed in the previous groups. An interesting phenomenon that begins to become evident in this class of patient is the tendency for changes to take place in the regions of the ureteral orifices, the same changes becoming obvious in these areas as are seen in the lower bladder fields. The most remarkable of these findings is the noting of a more marked change in the region around the ureteral orifice on the side toward which the occiput of the fetus had been directed (Fig. 3).

4. Here we are dealing with the average primigravida in whom the fetal head is engaged previous to and throughout labor, and whose labor consumes an average length of time. In this group there is the regular finding of more

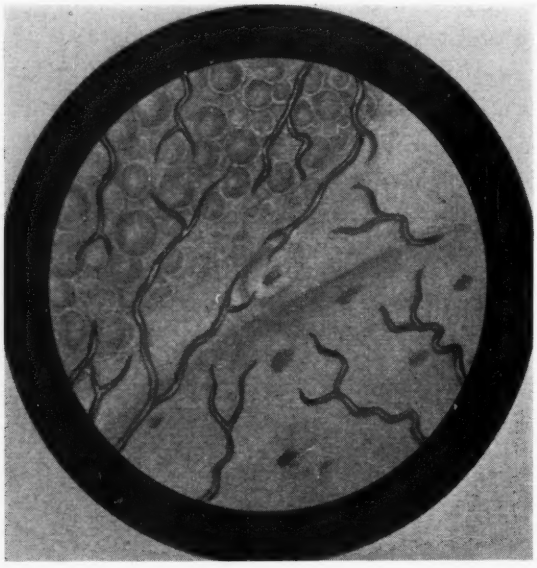

Fig. 3 (Groups 3 and 4).—Edema of ureter with hyperemia and submucosal hemorrhage in area around the ureteral orifice.

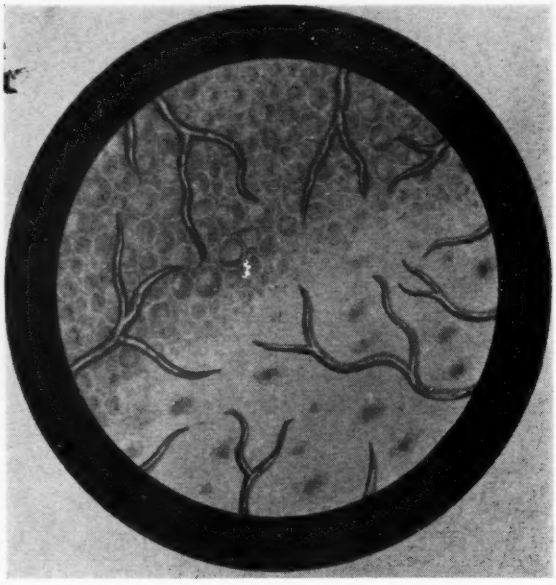

Fig. 4 (Groups 3 and 4).—Increasing amounts of edema, hyperemia, engorgement of vessels, and more pronounced submucosal hemorrhages.

extensive submucosal hemorrhage in both the regions of the lower bladder and around the ureteral openings. The edema is much more marked, reaching the proportion of bulla formation in some instances. The patient with an average uncomplicated breech delivery and the patient delivered by the application of low forceps also fall into this group (Fig. 4).

5. This group includes the patients with prolonged labors and those delivered by difficult instrumental or manipulative procedures. The bladders of these women showed further evidence of trauma, the most distinctive findings being large plaquelike areas of submucosal hemorrhage with actual capillary oozing into the bladder cavity. In the most severe instances, this took the form of hemorrhage sufficient to produce gross hematuria. The edema of the lower bladder area and the regions around and between the ureteral orifices becomes so marked as to make these openings greatly elevated and give them the appearance of being almost occluded. In addition, the marked injection and the submucosal hemorrhagic areas extend up the side walls of the bladder for a distance far beyond that seen in any other of our groupings (Fig. 5).

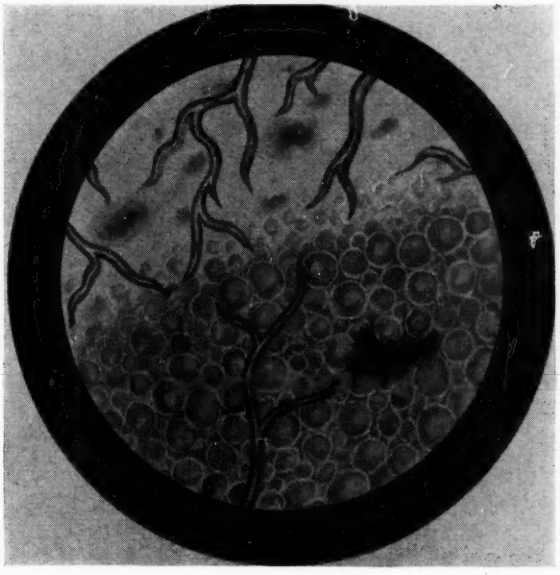

Fig. 5.—Large plaques of submucosal hemorrhage with free bleeding into the bladder.

Comment

A study of these cystoscopic findings can leave no doubt in our minds that labor and delivery have a definite effect upon the urinary bladder. That this effect, in most instances, is rather evanescent can be deduced when our findings are compared to those of Bennetts and Judd who performed their cystoscopic examinations 36 to 72 hours post partum. These authors reported "... evidence of ecchymosis such as might be expected from direct trauma" in only 16 per cent of their cases. In the few patients in our series who were re-examined 48 to 72 hours post partum, we found that the marked changes seen immediately after delivery regress toward normal very quickly. The urinary bladder evidently possesses tremendous recuperative powers up to the point where the compression of this organ between the fetal head and the maternal bony structures may produce true necrosis and vesicovaginal fistula. Nevertheless, we must face the possibility of such complications arising as a result of undue trauma to the bladder in prolonged or neglected labor.

The bladder of the pregnant woman at term and not in labor shows certain deviations from normal which are not extensive. There is some generalized edema and a slightly increased hyperemia as a result of the excessive passive congestion and vascularity seen in all pelvic structures at this time. The changes that follow as the patient goes into labor are progressive and directly proportionate to the length of labor, the length of time that the fetal head is engaged in the maternal pelvis, the tightness of fit between the head and the pelvis, the position of the fetal head on engagement and while it is descending through the maternal pelvis, and the type of delivery which terminates the second stage of labor.

A rapid multiparous labor with a short second stage, where the fetal head descends into and through the mother's pelvis in a matter of minutes, results in very minimal bladder trauma and visible change. As labors get longer, particularly where the fetal head is engaged in the pelvis and is in occiput posterior position, there is more and more evidence of insult to the bladder. This is very marked, as would be expected, in those patients who fall into the category of prolonged labor, and most noticeable in the cases where long labor is terminated by difficult midforceps delivery. This is contrary to the findings of Bennetts and Judd who state, "It would be reasonable to assume that bladder trauma would be increased in prolonged labor, in difficult forceps deliveries, or in breech deliveries with pressure from above on the aftercoming head. However, a comparison of the 7 breech deliveries with the group of 105 cases originally examined showed no higher incidence of direct bladder trauma. This was also borne out in the two cases of midforceps, the cesarean section and the version and extraction." We cannot corroborate these conclusions in view of our findings.

The progressive changes in the bladder are seen principally in the regions of the trigone, the ureteral orifices, and the interureteral ridge. These alterations consist of increased amounts of edema, hyperemia, submucosal hemorrhage, bulla formation, and finally hemorrhage, varying from petechial to rather massive with actual oozing of blood into the bladder cavity. In the most severe instances, the noticeable changes go beyond the areas already mentioned and reach along the sides of the bladder almost to the dome.

Summary

Evidence obtained on cystoscopic examination of 71 patients studied immediately after delivery leads us to conclude that the urinary bladder is definitely insulted during the course of labor. This insult is directly proportionate to the length of labor and the trauma of operative delivery. From this we can see that prolonged or neglected labor and very difficult forceps deliveries, amounting to so-called obstetrical victories, may produce permanent injury to the bladder in the form of pressure necrosis or direct traumatic laceration.

The possibility of resulting fistula formation leads us to feel that in weighing the indications for cesarean section in prolonged or potentially prolonged labor, the bladder may become one of our chief points of concern.

In order to estimate better the condition of the urinary bladder we suggest that, following prolonged labor or difficult operative or manipulative delivery,

the patient be catheterized. If there is gross blood in the urine, it denotes severe trauma and cystoscopy is indicated at once to determine the exact status of the bladder. If there is laceration, suitable measures must be taken. If no irreversible trauma is found, an indwelling catheter should be inserted and allowed to remain in place until the hematuria disappears.

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30 North Michigan Avenue (Dr. Klawans)

Discussion

DR. HERMAN I. KANTOR, Dallas, Texas.—Progress in medicine is often accomplished when we can step back to restudy some situations we have been accustomed to accept as factual.

There are many physiologic changes which we acknowledge and teach as the normal preparations for delivery. Hydremia, transient ligament and muscular relaxations, uterine changes with the development of the lower uterine segment are good examples. The decrease in tone of the bladder musculature is another. As a result, its capacity is increased considerably and there is diminished sensitivity to intravesical fluid tension. Undoubtedly, this hypotonicity results in lessening the severity of injury to the bladder during the process of delivery.

Two facts are outstanding in this study of the postpartum bladder. First, *every* patient presents evidence of trauma to the bladder after delivery. As a matter of fact, edema and hyperemia of the mucosa are seen even before labor starts. Second, these findings tend to disappear rapidly during the first few postpartum days. The question which must be raised, then, is, Where is the dividing line between physiologic and pathologic change?

For some time we have been teaching that *routine* catheterization before delivery is unnecessary, and may even result in additional bladder trauma. In order to try to prove this point, a number of patients to be delivered spontaneously or by outlet forceps were divided into two groups. In the first, catheterization was performed routinely before delivery. In the second this procedure was omitted. Cystoscopy was done during the first 24 hours following delivery. *No* consistent differences could be found between these groups. In both, the appearance of the bladder mucosa with edema, hyperemia, and small hemorrhages was identical with the findings described by the authors of this paper. The advantages of omitting catheterization as a predelivery routine could not be demonstrated in this way because we now believe these findings are physiologic. They are certainly constant sequelae of labor and delivery, and they are not eliminated by cesarean section. It is perhaps possible that this minor trauma may serve a useful function toward hastening the return of normal bladder tone.

On the other hand, exaggeration of this trauma may result in bladder lacerations, fistulas, and undue permanent relaxation of the perivesical ligaments and fascia. These are the pathologic manifestations of forceful and usually unfortunate obstetric management. They are the aftermath of a difficult tug of war. Even though the obstetrician may finish on his stool, both mother and fetus often bear the scars of his ego plus his amazing athletic prowess. As the authors have stated, they represent not a triumph but a placard of poor judgment.

DR. JOHN F. WOLFF, Chicago, Ill.—Some ten years ago the incidence of postpartum pyelitis seemed to be quite high, at least in my small practice, and I went about trying to find a prevention for it in a most left-handed manner as compared to that of Dr. Klawans and Dr. Kantor, namely, taking the cases of postpartum pyelitis I saw.

I noticed, as many of you have, that it always followed repeated catheterizations immediately post partum. This usually was due to the fact that there was so much urinary retention. The first or second catheterization often yielded 750 to 1,200 c.c. of urine.

In an attempt to prevent this, at that time the Hopkins group were instilling Mercurochrome in the bladder. At first the method appeared promising but, as many of you found out, it did not work too well. Then the method that Dr. Kantor mentioned was tried, that of inserting an indwelling catheter. When that was done the postpartum complication disappeared to some extent, but the patients were quite uncomfortable with the catheter in place.

Going back over the histories, we found that repeated catheterizations always followed (as Dr. Klawans mentioned) cases of prolonged labor and the difficult type of operative obstetrical maneuvers. When the use of the catheter was limited to those patients, it seemed to lower the incidence of postpartum complications.

Just about that time we began permitting our patients to get out of bed earlier. When that was done, the incidence of postpartum complications of the bladder seemed to be lowered greatly. I have noticed in the past year that there was only one patient on our small service who had to be transferred off the floor on account of morbidity from postpartum pyelitis. Getting the patients up in a normal and comfortable position sometimes prevents urinary retention, as you know.

I would like to ask Dr. Klawans if he has done any cystoscopic studies of patients following gynecologic surgery, especially the bladder plastic operations, because certainly that is a troublesome type of thing to all of us.

DR. KLAWANS (Closing).—To answer Dr. Wolff's question, we are contemplating a series of studies, and one of them will be a study of the postoperative bladder immediately following surgery. We have had slight difficulty, not real difficulty but discomfort, in getting our nurses to hold still for the cystoscopy. They have got to sterilize other apparatus, and they have to spend an extra half hour or so in the delivery room, and it will be the same in the operating room; if we can persuade our nurses to bear with us, we may be able to carry out this procedure.

Dr. Priest, of Presbyterian Hospital, has had this in mind for a long time, and we are going to try to carry it through. We are also planning with this a study of the urinary tract by intravenous pyelography immediately before and immediately following surgery. We may find some things that will turn our faces red, although I do not know.

Dr. Wolff spoke about early ambulation as an aid in emptying the bladder. We have found that the cystoscopy did not interfere one bit with early ambulation. The patients got up on the second day, just as ordinary patients do. We had no febrile reactions. We think there is no objection to a cystoscopy following delivery.

RARE MESODERMAL TUMORS OF THE UTERUS AND VAGINA*

DAVID A. BICKEL, M.D., AND JENE R. BENNETT, M.D., SOUTH BEND, IND.

(From the South Bend Medical Foundation)

TUMORS of the urogenital tract, which are thought to arise from mesodermal tissue displaced during embryonic development, have been rarely reported until recently. It is thought that these mesodermal elements are carried along with the embryonic structures normally destined to form the lower genital and urinary tracts. Such tumors, because of their tentatively supposed histogenesis, are described as dysontogenetic tumors. The extreme histologic variation presented by this group of tumors renders standard pathologic interpretation and standard descriptive nomenclature and classification very difficult. The history of this ill-defined group of neoplasms and a review of the literature has been amply presented in several recent reports.[1, 2, 3] In this paper are presented two highly malignant tumors, one of the uterus and one of the vagina, and a benign lipomatous tumor of the uterus. These tumors may be considered as examples of dysontogenetic tumors.

CASE 1.—This patient was a nulliparous white woman 73 years old. Her past history revealed no serious illnesses or operations. The menopause had occurred when she was 47 years old, and she had no symptoms of pelvic disease until the present illness. She had noticed scanty irregular vaginal bleeding for three months before admission to the hospital, June 20, 1951. The general physical examination and routine laboratory tests were negative. Pelvic examination revealed a normal nulliparous cervix and a uterus about the size of a three months' gestation which was symmetrical, firm, and easily movable. There were no palpable adnexal masses. A diagnostic curettage was performed. The uterine cavity was found to be small, and the tissue obtained was insufficient for histologic examination. At this time, 40 mg. of radium was inserted into the uterine cavity for 95 hours—3,800 mg. hr. of intrauterine irradiation. On July 24, 1951, about four weeks later, the uterus, tubes, and ovaries were removed. The pelvis was free of adhesions, and none of the pelvic nodes appeared enlarged or indurated.

The report of the pathologic examination of the removed tissue was as follows: The specimen consisted of a uterus with cervix, tubes, and ovaries. The tubes and ovaries were grossly normal. The body of the uterus was deformed and enlarged by multiple intramural and subserous tumors of white glistening appearance. One tumor was 10 cm. in diameter and was unusual in that it was soft, homogeneous, and showed areas of hemorrhage and degeneration. The uterine cavity was distorted by the tumors but lined by an intact atrophic endometrium.

Microscopic examination of the largest myometrial tumor revealed an unusual histologic pattern. The connective tissue stroma which predominated contained numerous multinucleate giant cells (Fig. 1). The pattern and cytology were identical to those of tumors commonly designated as "giant-cell tumors of tendon." However, this tissue showed a gradual transition to areas of clear-cut cartilage and osteoid tissue (Fig. 2). Histologic sections of the endometrium, cervix, tubes, and ovaries were without evidence of tumor or other significant abnormality. The other uterine tumors were typical leiomyomas. At this time, a diagnosis of osteoid metaplasia in a leiomyoma was made.

*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

The patient was in good health, and there was no evidence of recurrence of the tumor until one year following its removal, when a painful nodule appeared on the right parietal bone, and also, at this time, the patient complained of pain in the right hip. Roentgenologic examination revealed extensive neoplastic bone destruction of the skull and right ilium, but no evidence of tumor in the long bones or lungs. Biopsy of the tumor growth in the skull revealed the same histologic picture as the uterine tumor, but without osteoid or cartilage formation (Fig. 3). These skeletal manifestations of the neoplasm became enormous before the patient's death, March 11, 1953. Autopsy was not obtained.

Comment.—Roentgenologic examination of the bony structures at the time of the removal of the uterus would have been important in the study of this case, since the primary site of the neoplasm has presented a question of pathologic interest. Tissues from the uterine tumor and from the later-occurring lesions of the bones have been studied by several pathologists and found to be of similar histologic structure, but there was divergence of opinion regarding the primary site of the neoplasm. One group of pathologists[4] who examined tissue from the original tumor doubted that it really came from a uterine tumor. However, when additional tissue from the tumor was examined, their report in part was as follows: "These findings are interpreted as a metaplastic or heteroplastic development in a leiomyoma in which some of the cellular elements are exhibiting the pluripotential states of mesenchymal derivatives. There is some osteoid matrix, and the giant cells resemble osteoclasts."

The biopsy material from the metastatic lesion in the right parietal bone, which was obtained one year after the hysterectomy was performed, was again sent to several consultants. The opinion of one consultant was: "In view of the clinical course of the patient, the uterine tumor was not the primary lesion, but was a metastasis from a primary occult neoplasm of bone, or possibly a so-called giant cell sarcoma of fascial origin."

If a skeletal osteogenic sarcoma did metastasize to the myometrium, it would be a very rare site of spread of this tumor. Osteogenic neoplasms arising in the urogenital organs have been reported with sufficient frequency to consider the uterus in this case as the more probable primary site. The formation of cartilage, osteoid tissue, and bone has been observed in uterine tumors, and metastases to bone have been reported.

CASE 2.—A 59-year-old white woman, gravida i, para i, was admitted to Memorial Hospital, South Bend, Ind., on Nov. 11, 1950. Her complaints were a scanty blood vaginal discharge and soreness of the right side of the vulva which extended into the vagina. She had had no previous serious illnesses or operations, but had experienced some dysmenorrhea throughout her mature years. Menstruation had ceased ten years previously. Following estrogen therapy two years prior to the present illness, there was slight uterine bleeding, at which time pelvic examination was negative, and cytology did not reveal malignant cells. This bleeding ceased when estrogen therapy was discontinued. Examination at the time of admission to the hospital revealed a small linear ulcerated area on the right vaginal wall. Beneath this area was a firm fixed tumor which extended diffusely beneath the bladder almost to the urethral orifice, and also into the right vaginal fornix. The cervix was normal, and the uterus was not enlarged; there were no adnexal tumors. The inguinal nodes were not palpable. Urine examination was negative; the blood serology was negative; erythrocytes 4.4 million per cubic millimeter, and hemoglobin 12.2 Gm. per cent. No malignant cells were found in the vaginal secretions. At operation, it was evident that total removal of the tumor was not possible, but a portion of it was removed for pathologic examination. The tissue had a uniform gray color on cut section, and was of a consistency frequently described as "fish-flesh."

Microscopic examination revealed the neoplasm to be made up of undifferentiated cells of sarcomatous pattern. The tumor cells were uniformly dispersed throughout the tissue and showed no organoid arrangement. These cells were pleomorphic with large rounded vesicular nuclei, although mitoses were not numerous. The histologic pattern suggested a tumor of the malignant lymphoma group (Fig. 4). No diagnostic features of Hodgkin's disease were seen. Reticulum stains showed an abundance of reticular network (Fig. 5).

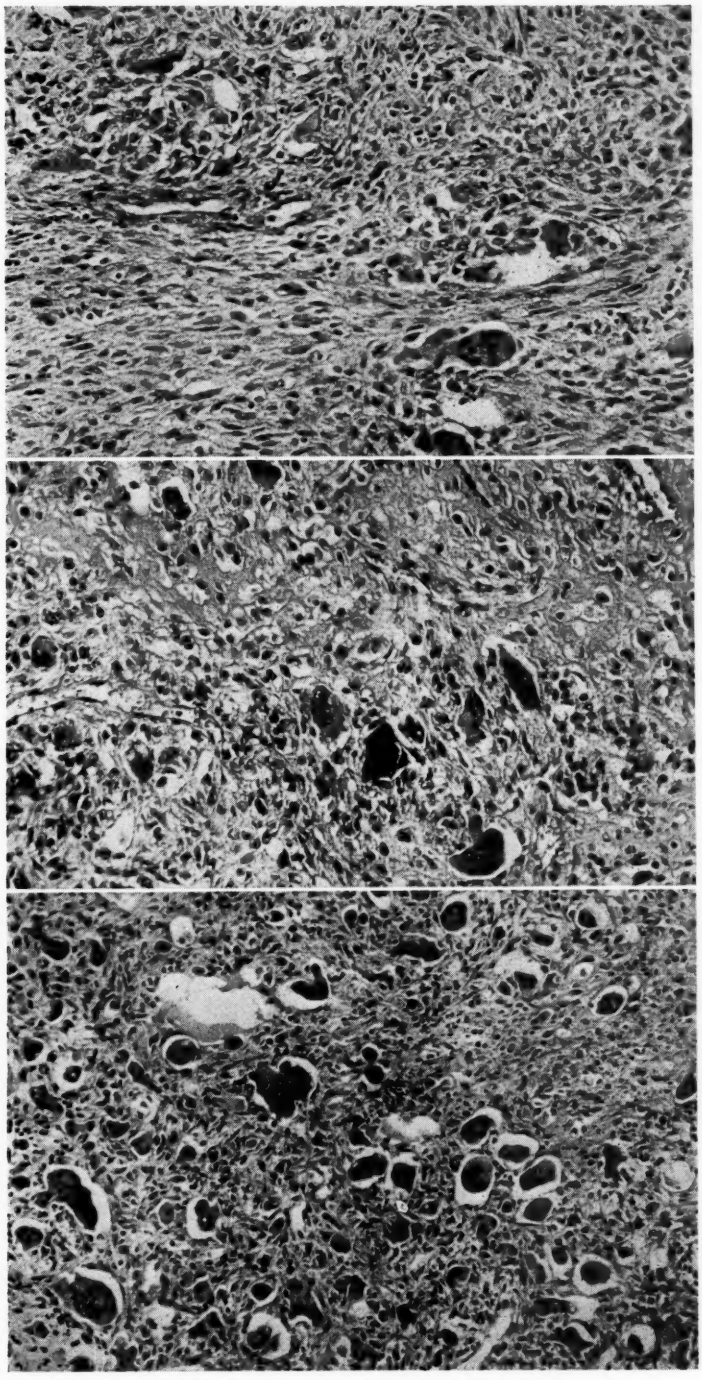

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1 (Case 1).—Uterine tumor showing numerous giant cells.
Fig. 2 (Case 1).—Uterine tumor showing area of precartilaginous structure.
Fig. 3 (Case 1).—Biopsy of metastasis to right parietal bone.

Diagnosis: Reticulum-cell sarcoma.

Treatment consisted of intensive x-ray therapy which had no effect on the growth of the tumor, and the patient died about six months following the operation. Autopsy was not obtained; consequently, the extent of the growth and the sites of metastases were not determined.

Fig. 4.

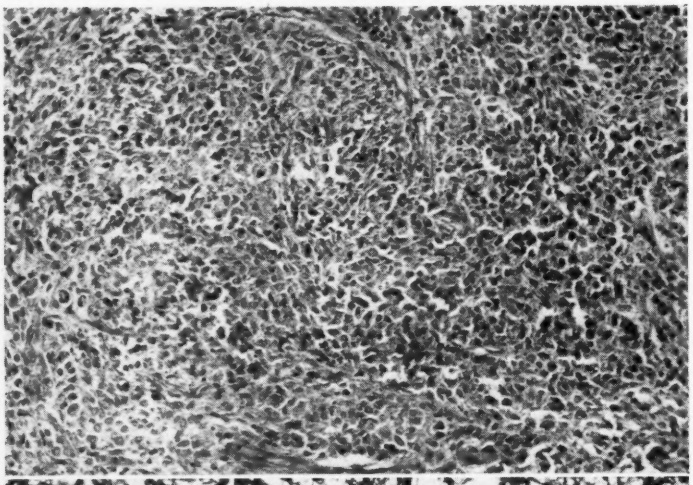

Fig. 5.

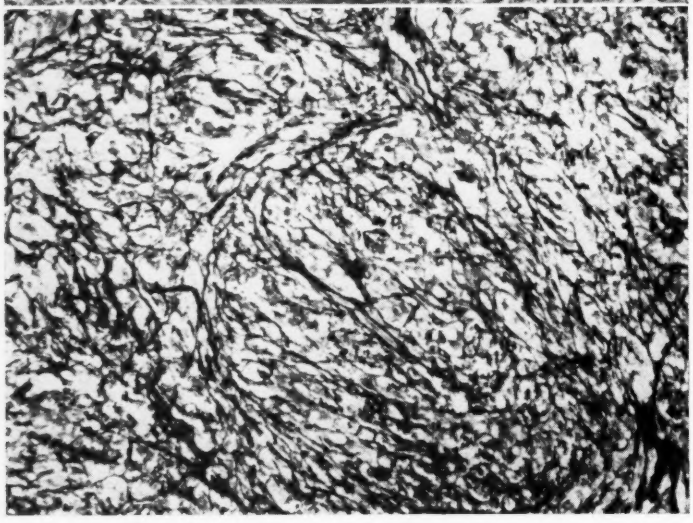

Fig. 4 (Case 2).—Vaginal sarcoma.
Fig. 5 (Case 2).—Vaginal sarcoma, reticulum stain.

Comment.—

Sarcoma of the vagina is one of the most rare and also one of the most malignant of pelvic tumors. The reported cases have been principally in infants and younger children.[5, 6] Characteristically, the tumors reported in children present a structure resembling a cluster of grapes; this gross appearance suggested the name botryoid sarcoma. The vaginal sarcomas which have been reported in adults have made their appearance in older women, mostly in the sixth and seventh decades of life. These highly malignant neoplasms, like the uterine tumor reported here, are now thought to arise from residual mesodermal elements, placing them in the dysontogenetic group.

CASE 3.—A 55-year-old white multiparous woman was admitted to St. Joseph Hospital, Mishawaka, Ind., June 5, 1952. Two years before admission, she had noticed a firm painless tumor in the lower abdomen which gradually increased in size. There were no other complaints referable to the pelvic organs. She had had no serious illnesses or operations, and the menopause had occurred nine years previously. On examination, a firm symmetrical movable tumor, about the size of a four months' pregnancy, was found which appeared to involve the uterus. The routine laboratory examinations were negative. At operation, the uterus was found to be the size of a four months' gestation and was soft and movable. There were no peritoneal adhesions, and the adnexa appeared normal. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The pathologic description of this specimen was as follows: The uterus with cervix, tubes, and ovaries attached weighed 1,000 grams. The uterus was soft, smooth, and symmetrically enlarged. A large intramural tumor measuring 15 cm. in diameter was present. The cervix, endometrium, tubes, and ovaries were grossly normal.

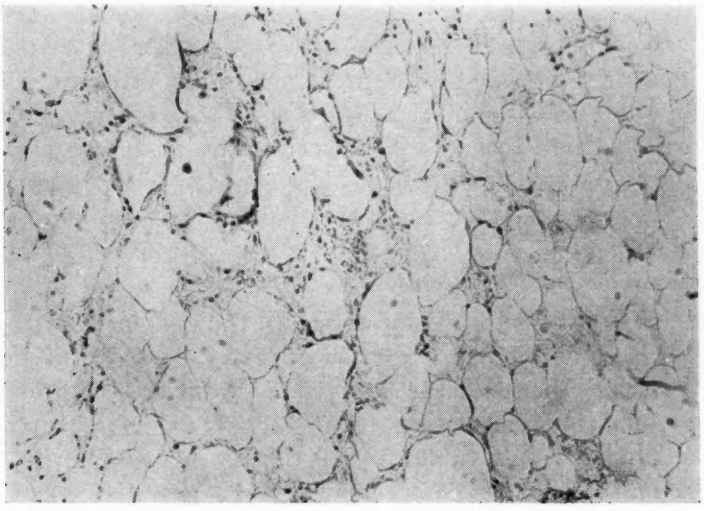

Fig. 6 (Case 3).—Uterine tumor showing lipomatous structure.

Microscopic examination of the uterine tumor revealed it to be composed predominantly of mature adipose tissue in which were hyalinized fibrous trabeculae (Fig. 6). The endometrium was atrophic. Sections of the cervix, tubes, and ovaries showed no unusual features.

Comment.—

Lipoma of the uterus is a rare benign tumor of little clinical significance. Because of the supposed histogenesis of this neoplasm, it is included in the group of dysontogenetic tumors. Previously, these tumors were thought to represent a degenerative process occurring in uterine myomas, but such an origin is unlikely since they are made up of characteristic fat cells and not merely lipid substance. Adipose tissue is not normally found in the uterus. Metaplasia of smooth muscle into fat cells has been suggested but the idea has not been generally accepted. Since adipose tissue is sometimes found associated with muscle and other heterologous tissues in so-called mixed mesodermal tumors, most authors ascribe the origin of the uterine lipomas to embryonic cell rests.

General Comment

The description of tumors of this group has been confused by a complex nomenclature. McFarland[7] found 119 terms in the literature which had been used to designate uncommon malignant neoplasms, which he considered to

arise from misplaced mesodermal elements, occurring in the urogenital region. Confusion has surrounded their true pathologic nature as well as their histogenesis. In general, they have in the past been designated as sarcomas and carcinosarcomas, but now they are considered in a group known as dysontogenetic tumors. Formerly these tumors were considered by most pathologists to develop as the result of neoplastic metaplasia. The theory of Hansemann, expressed by Nicholson,[8] proposes that when normal cells embark on malignant growth, they demonstrate various stages of dedifferentiation, sometimes to a degree of displaying embryonal characteristics. In support of this theory, it has been recognized that extraskeletal osteogenic tumors may develop by a process of metaplasia in various types of tumors.[9] However, it is now considered likely, but not proved, that both simple and heterologous neoplasms belonging to this group have their origin in dislocated mesodermal tissues associated with the Müllerian system.[7] There is considerable evidence for the presumption that, if the embryonal tissue is of a single cell type, histologically simple tumors will result, but if these embryonal fragments are composed of cells with pluripotential capacity for differentiation, so-called mixed mesodermal tumors can be derived from them.[7] The term "mesenchymoma" has been suggested for tumors of mesodermal derivation.[10] The tumor in Case 1, which included cartilage and osteoid tissue without the presence of striated muscle, would not be classified by some pathologists as a mixed mesodermal tumor.[11]

In the case of the vaginal sarcoma (Case 2), the histologic features, demonstrating abundant reticular fibers, influenced us to classify it as a reticulum-cell sarcoma rather than to use the term "sarcoma, unclassified." It might be said that one need not resort to the dysontogenetic theory to explain the origin of such a tumor in any tissue in view of the widespread distribution of the reticuloendothelial tissues in the body. However, the rarity of this type of tumor of the vagina is in itself evidence of the need for a special theory of histogenesis as contrasted to that employed for the tumor when it develops in the common sites of reticulum tissue. If the osteogenic uterine tumor (Case 1) developed in close relationship to bone or periosteum, there would have been no need to resort to a dysontogenetic theory of origin. The purpose of this paper is not to prove or to disprove any special histogenic theory but rather to report these tumors of unusual histologic structure.

The treatment of malignant dysontogenetic tumors is most discouraging. When discovered, they are beyond the possibility of surgical removal, and they do not respond to radiotherapy with any degree of regularity.

Summary

Three cases of mesodermal tumors of the uterus and vagina are presented: an osteogenic uterine tumor of complex histologic structure; a reticulum-cell sarcoma of the vagina; and a benign lipoma of the uterus. The hypotheses of the histogenesis of this group of neoplasms, namely, metaplasia and dysontogenesis, are discussed. Since a considerable number of these tumors have been recently reported, it is likely that they are not as rare as was formerly believed.

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Discussion

DR. JOHN A. WALL, Houston, Texas.—We are at once impressed that the nomenclature is, indeed, highly confusing. Unquestionably, in many instances, a highly anaplastic adenocarcinoma of the endometrium cannot easily be distinguished from a sarcoma. We have recently had such an instance in which sarcomatous changes in a highly anaplastic adenocarcinoma of the endometrium were diagnosed by several well-recognized pathologists. Sarcomas of the uterus are highly fatal and the prognosis in the individual case is indeed unpredictable. The fact that these lesions are relatively rare, and the difficulty of classification, and the improbability of acquiring a statistically significant number of them for comparison make it impossible to be dogmatic about what can be expected.

Irradiation might be considered as a means of controlling the epitheliomatous components and its use may outweight the disadvantages of postponing operation. Our use of preoperative irradiation is usually based on such histological interpretation, where the epithelial characteristics seem to be definitely predominant. At operation, whether irradiation has or has not been employed preoperatively, the cervix is sutured and a radical hysterectomy with lymphadenectomy is performed. The radical lymphadenectomy is considered an integral part of the operation because of our experience with two cases which had metastasis to lymph nodes. A third case had demonstrable endometrial extension to the lymph nodes. In this particular instance, the pathological opinion was divided between sarcoma and highly anaplastic adenocarcinoma in the primary lesion.

Our group of 8 cases shows the generally recognized confusion of terminology. We have had 5 mixed mesodermal tumors, 2 of which were classified as sarcoma botryoides; one stromal sarcoma, one leiomyoma sarcoma, and one which was called "unclassified malignant tumor, suggests mixed mesodermal tumor."

It might be well to mention here that in addition to the aforementioned 8, 2 other patients have had 2 separate or mixed primaries. One showed a squamous-cell carcinoma of the cervix and adenocarcinoma of the endocervix and the other a sarcoma and adenocarcinoma of the endometrium.

The average age of these patients, which is significant, was 60 plus years in our series. Only two patients under the age of 50 years were encountered; one of these had a leiomyoma sarcoma, and the other an unclassified lesion which we thought was suggestive of mesodermal tumor.

Four of our patients have died within six months to a year. We have had one patient whom we have followed for one year, 2 have been followed from 1 to 2 years, and both of these showed stromal sarcoma. One patient with the leiomyoma sarcoma has been followed for four years and is well up to this date. The 2 patients with the mixed primaries have been operated on during the past three months, and the end result cannot be discussed.

The treatment instituted in our group varied. Two patients had surgery alone and one of these patients was operated on prior to admission to The M. D. Anderson Hospital for Cancer Research; 3 patients have had irradiation fol ved by surgery, and 3 patients have been discharged as in terminal condition.

I believe these tumors will become more frequently recognized as more tissues are subjected to histological evaluation in smaller community hospitals as well as in the larger urban centers and their true entity established. Extension of operability to include patients formerly classified as inoperable permits more accurate classification of mesodermal tumors both clinically and pathologically.

DR. BENNETT (Closing).—I want to thank Dr. Wall for the work he has done in collecting the cases in his own experience. We are not going to settle the histogenesis of this group of neoplasms for a long time, in my opinion. Classification, of course, is consequently very difficult.

We have not included carcinosarcomas in this paper because there is so much difference of opinion as to whether or not they really exist as carcinosarcomas, or whether they are just very undifferentiated anaplastic carcinomas.

PELVIC PAIN OF GYNECIC OR OTHER ORIGIN*

WILLIAM F. GUERRIERO, M.D., AND JOHN STUART, M.D., DALLAS, TEXAS

WOMEN seek medical aid during the reproductive period for complaints that they localize as originating from disease of the reproductive organs.

The chief complaint of 5,539 patients† admitted to our observation was pain in the region of the pelvis in 1,371 cases, either of gynecic origin or simulating such pain.

From such men as White,[13] Wilson and Mussey,[1] Bentley,[11] Smithwick,[10] Theobald,[2] Ruch,[3] Wolff and Hardy,[9] Wolf and Wolff,[17] and others, we have gained a knowledge of the basic anatomy of the nervous pathways and the physiology involved in the production of gynecic pelvic pain and pain apparently of other origin.

This pain may be somatic, visceral, or a combination of both in origin. Of the somatic system, we are concerned only with the sensory nerve supply. In the region of the pelvis, this is furnished by the lumbosacral plexus, which is formed by a fusion of the anterior rami from the lumbosacral portion of the spinal cord and the coccygeal nerve.

From Fig. 1 can be seen the extensive sensory nerve distribution of the pelvic area from the lumbosacral plexus. A further division of this plexus and the specific areas served by sensory nerve branches are as follows:

LUMBOSACRAL PLEXUS

(ANTERIOR BRANCHES L1, L2, L3, L4, L5, S1, S2, S3, S4)

A. Muscular branches
   1. Quadratus lumborum
   2. Psoas major and minor
B. Iliohypogastric
   1. Muscles: transversus abdominis and internal oblique
   2. Peritoneum
   3. Cutaneous areas over lateral and upper portions of iliac crest
C. Ilio-inguinal
   1. Abdominal muscles
   2. Peritoneum
   3. Cutaneous areas of upper and medial parts of thighs, mons pubis, and labia majora
D. Obturator
   1. A direct branch to external obturator muscle
   2. Anterior and posterior terminal branches to abductor muscles and cutaneous surfaces of medial aspect of thigh
   3. Branch to hip joint from anterior branch

*Presented at the twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

†From the private obstetric-gynecologic practice of William F. Guerriero, M.D., V. A. Davidson, M.D., and John Stuart, M.D.

SACRAL PLEXUS

(ANTERIOR BRANCHES L4, L5, S1, S2, S3)

A. Muscular branches
   1. Pyriformis
   2. Obturator internus
   3. Gemelli and quadratus femoris
   4. Gluteal muscles
B. Cutaneous areas
   1. Lower and lateral portions of buttocks
   2. Perineum and posterior surfaces of labia majora

PUDENDAL PLEXUS (PART SACRAL PLEXUS)

(ANTERIOR BRANCHES S1, S2, S3, S4)

A. Muscular branches
   1. Levator ani and coccygeal
B. Visceral branches (middle hemorrhoidal, inferior vesical, and vaginal nerves)
   1. Rectum
   2. Vagina
   3. Bladder
C. Pudendal nerve supplies
   1. External anal sphincter
   2. Anal skin, labia majora and minora
   3. Skin of perineum and labia majora
   4. Superficial transverse perineal muscles
   5. Bulbocavernosus
   6. Deep transverse perineal
   7. Urethral sphincters
   8. Clitoris

Further somatic innervation of the anterior abdominal wall by cutaneous sensory nerves is exhibited in Fig. 2. This is clinically important in referred cutaneous pain which simulates deep pain in origin and is often called somatic pain of the anterior abdominal wall.

The visceral innervation is effected by the autonomic, or involuntary nervous system. Of this system, we are primarily concerned with the sacral autonomic or parasympathetic and the thoracolumbar autonomic or sympathetic systems.

The autonomic system has afferent fibers which have a fundamental arrangement like the somatic neurons. The nutrient cells for the afferent fibers are found in the posterior root ganglions. These fibers from the viscera are carried in the autonomic system entering the spinal cord in the posterior nerve roots and are now accepted as being sensory fibers merely in an autonomic system. Fig. 3 gives a graphic illustration of these sensory afferent fibers from the viscera concerned with gynecic and similar pain.

The following gives a description of the areas of referred pain from this nervous system:

The Cervix and Lower Uterine Segment.—The area of referred pain consists of (a) the sacral area of the back, (b) the buttocks, and (c) the back of the thighs and legs as far as the heel.

The Body of the Uterus and Uterine Tubes.—The area of referred pain consists of the lower part of the abdominal wall from below the umbilicus to the groins, the "tubo-ovarian triangle" on each side.

The Ovary and Outer One-Third of the Tube.—The area of referred pain is the anterior abdominal wall opposite and just below the umbilicus.

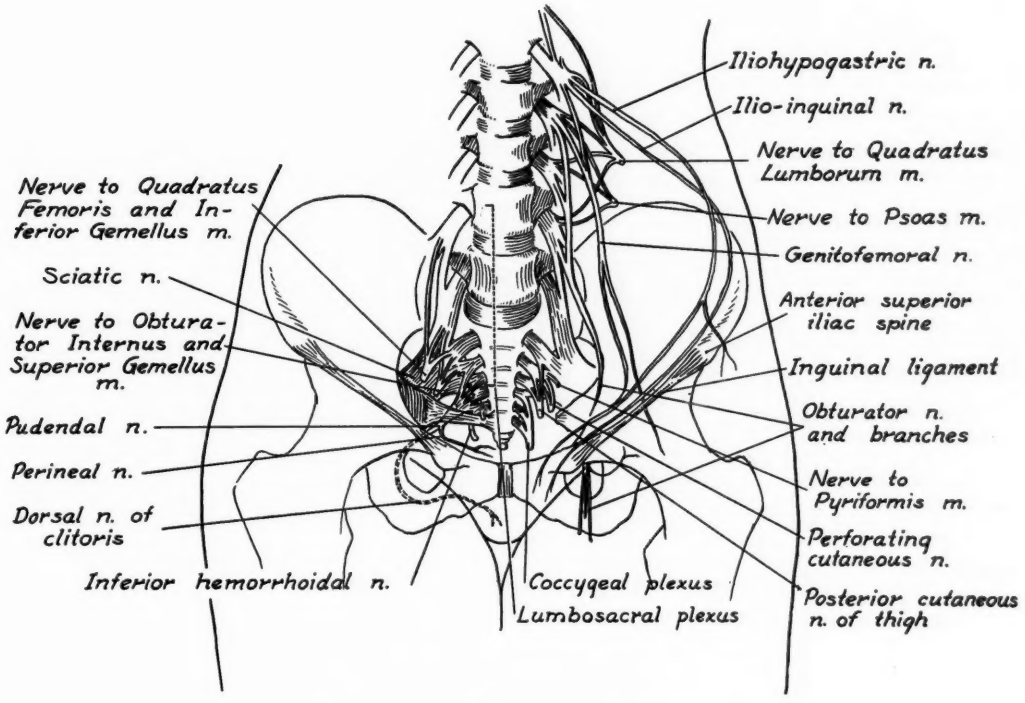

Fig. 1.

Bladder.—The area of referred pain from the trigone and urethra is (a) to the lower sacral area of the back, (b) to the buttocks and perineum, and (c) down the back of the thigh and leg to the heel. From the fundus it is to the lower part of the anterior abdominal wall above the pubis and the groins.

Rectum.—The area of referred pain is the lower sacral area, the buttocks, and the back of the thighs and legs.

The Peritoneum.—The visceral peritoneum is insensitive to local stimuli such as pricking, cutting, or pinching. But any pull on a mesentery attaching a viscus to the abdominal wall causes pain. However, recent work[17] has shown that under appropriate stimuli both the mucosa and the deeper structures of the gut are sensitive to pain.

The larger arteries of the mesenteries and the parietal peritoneum are sensitive to pain. A pull from traction will cause pain, due probably to pull on the arteries.

The parietal peritoneum is said to be very sensitive. But it is not settled yet whether this is a quality of the inner smooth surface of the peritoneum or of the subserous connective tissue.

When the parietal peritoneum is inflamed or irritated, somatic nerves carry the pain to the spinal cord and cause the referred pain and muscle spasm that occur in the anterior abdominal wall in acute peritonitis.

The Pelvic Connective Tissue.—The pelvic viscera are closely surrounded by much loose connective tissue, which in pathological states is soon involved; for example, in inflammation or malignant disease of the organs. It is rich in sympathetic nerve fibers and also has some somatic nerve fibers from the internal pudendal nerve (second, third, and fourth sacral). Any irritating condition of the pelvic connective tissue causes the deep dull ache of visceral pain.

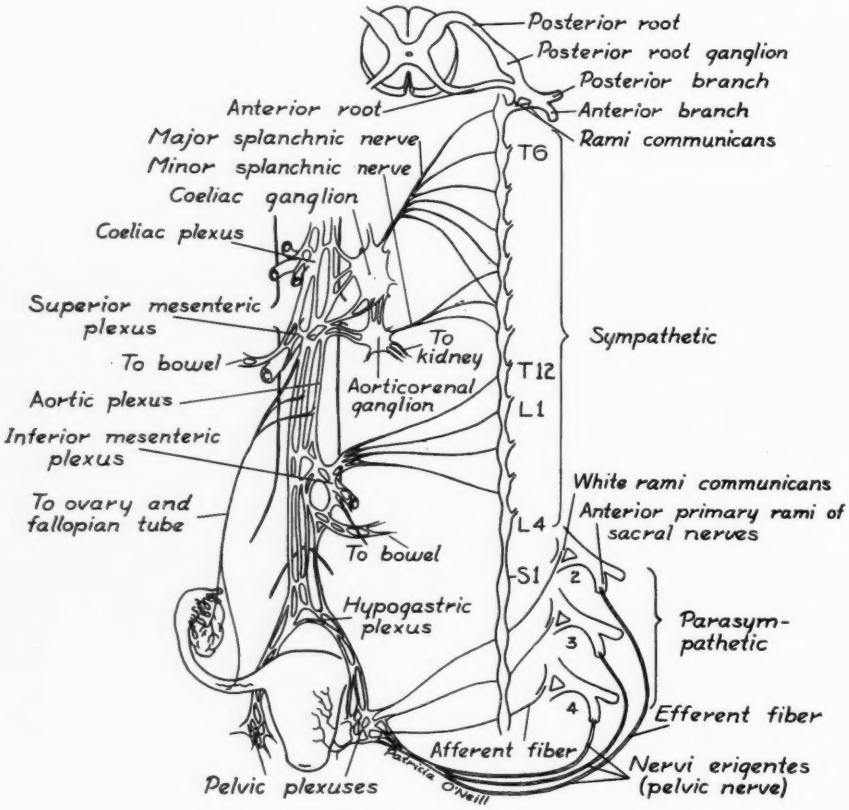

Fig. 2.—Gynecic autonomic nerve anatomy.

Concern with the stimulus of pain raises the question of its type, severity, quality, duration, and location. One can adequately evaluate these questions when somatic superficial structures are involved. However, when deeper structures and viscera are involved, these questions are difficult to answer.

In order to appreciate this difficulty in evaluating pain stimuli arising from viscera and deep structures, we must understand certain basic anatomic and physiologic principles.

Man has so little experience with visceral pain that he fails to build up an elaborate cortical projective pattern of the interior of his body. This is ex-

emplified in the newborn baby who cannot localize the source of superficial pain stimuli until such time as he is able to build up a cortical pattern of his superficial structures.

There may be a subthreshold of excitation of visceral sensory nerves so that a number of afferent impulses must be received by a central neuron before a stimulus is transmitted to the sensory cortex. Thus, subthreshold stimuli from a viscus may be impotent to produce pain. However, when combined with a somatic stimulus a pain stimulus results which is localized as of somatic origin, because the mind has a better projective pattern of the origin of somatic stimuli.

A subthreshold stimulus from the viscera and other deep structures may be received as a pain stimulus in the presence of anemia, disease, exhaustion, and inflammatory states.

It is now generally accepted that violent emotions produce vascular contractions of the vessels of internal organs which precipitate pain stimuli of threshold character.

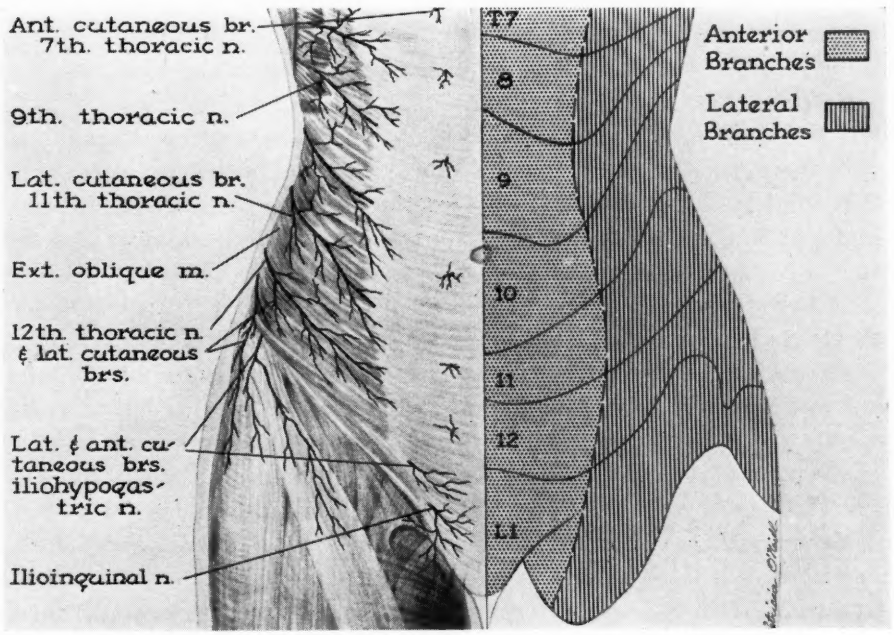

Fig. 3.

The basic physiologic stimulus of visceral pain is not burning, cutting, or crushing, but distention of unstriated muscles, as shown by Hertz.[2]

To conduct these pain stimuli the viscera, as well as other deep somatic structures, are supplied by fine, beaded terminals with nerve fibers having little or no myelin sheath and a relatively slow rate of conduction. These endings are relatively few in comparison to the many which supply the very pain-sensitive cutaneous structures, the cornea of the eye, and the periosteum of bone. There is also an absence in these deep structures of the differentiated nerve endings that are capable of appreciating temperature or touch which are

so prevalent in cutaneous structures. Weddell[12] showed that the ability to localize the source of a stimulus depends strictly on the richness and overlapping of these sensory terminals.

Visceral pain is now generally accepted as being direct or referred. Ross[5] thought that visceral pain had a direct "splanchnic" component consisting of a deep, poorly localized ache near the midline in the substernal, epigastric, or abdominal region. This supposition has repeatedly been verified by section of the splanchnic nerves supplying the viscera.[14] Referred visceral pain is more adequately explained on the basis of central misrepresentation of the source or to a viscerocutaneous reflex. For a more detailed discussion on the theories of referred pain the reader is referred to the works of Theobald,[2] Ruch,[3] and Wolff and Hardy.[9] The latter have divided the neurophysiologic mechanisms that underline the perception of pain from viscera and the deeper structures into two categories:

1. True Visceral and Deep Somatic Pain.—

True visceral and deep somatic pain is felt at the site of primary stimulation and may or may not be associated with referred pain. It is eliminated by infiltration of procaine into the site of noxious stimulation, or by blocking its afferent nerves; but it is not altered by infiltration of procaine into the other structures supplied by the same or adjacent neural segments.

2. Referred Pain.—

Referred pain may occur in addition to or in the absence of the true visceral and deep somatic pain just described. It is experienced at a site other than that of stimulation, but in tissues supplied by the same or adjacent neural segments. It may occur with or without associated hyperalgesia and hyperesthesia.

A. Referred Pain Without Superficial and/or Deep Hyperalgesia.—When pain occurs without superficial and/or deep hyperalgesia it depends only on the central effects of the spread of excitation of the original noxious impulses to the same and adjacent segments of the cord, whence they are relayed to higher centers for perception and interpretation. Injection of procaine into superficial or deep regions of referred pain does not reduce the intensity of pain due to this mechanism.

B. Referred Pain With Superficial and/or Deep Hyperalgesia.—Referred pain may be accentuated in intensity by virtue of the effects of ordinarily nonnoxious stimuli from zones of reference. Impulses from such sources, normally inadequate to produce pain, may do so upon reaching the cord in a segment involved in the central spread of excitation. Procaine injected into superficial or deep hyperalgesic structures will cause abolition of this element of the referred pain phenomenon, resulting in more or less reduction of the subject's discomfort, depending on the amount of hyperalgesia.

In view of the preceding known basic physiologic and anatomic factors it is easily realized how women find it difficult to determine the type, severity, quality, and especially location of pain stimuli emanating from pelvic viscera and other deep structures.

In these 1,371 women who had as their primary complaint pain which they localized as originating from disease of the reproductive organs, we found 800

cases, or 58.4 per cent, to have such an origin; while 571, or 41.6 per cent, had other origins. Our accepted etiology of the pain these women complained of after thorough observation and appropriate surveys is listed in Tables I-VIII.

TABLE I. ORIGIN OF PAIN SIMULATING GYNECIC PAIN IN 571 CASES

	NO. OF CASES	PER CENT
Genitourinary	246	43.8
Orthopedic	154	26.9
Gastrointestinal	149	26.0
Psychiatric	22	3.85
Total	571	100

TABLE II. GYNECIC PAIN IN 800 CASES

	NO. OF CASES	PER CENT
Organic	511	63.8
Nonorganic	289	36.2
Total	800	100

TABLE III. PAIN OF GENITOURINARY ORIGIN SIMULATING GYNECIC PAIN, 246 CASES

		NO. OF CASES	PER CENT
1. Urethra		146	59.3
a. Urethritis	104		
b. Strictures	24		
c. Polyps	11		
d. Diverticulum	7		
2. Bladder		4	1.62
a. Huhner's Ulcer	3		
b. Endometriosis	1		
3. Ureters		21	8.53
a. Congenital	3		
b. Stones	18		
4. Kidneys		75	30.4
a. Pyelonephritis	47		
b. Stones	6		
c. Pelvic	7		
d. Ptosed	6		
e. Congenital	9		
Total		246	100

TABLE IV. PAIN OF ORTHOPEDIC ORIGIN SIMULATING GYNECIC PAIN, 154 CASES

	NO. OF CASES	PER CENT
1. Posture	102	66.2
2. Mechanical	21	13.6
3. Congenital	18	11.6
4. Infection	13	8.44
Total	154	100

TABLE V. PAIN OF GASTROINTESTINAL ORIGIN SIMULATING GYNECIC PAIN, 149 CASES

	NO. OF CASES	PER CENT
1. Colitis	93	62.3
2. Appendicitis	27	18.0
3. Diverticula of colon	15	10.06
4. Cholelithiasis	9	6.16
5. Amebiasis	3	2.01
6. Meckel's diverticulum	1	.671
7. Duodenal ulcer	1	.671
Total	149	100

TABLE VI. PAIN OF PSYCHIATRIC ORIGIN SIMULATING GYNECIC PAIN, 22 CASES

	NO. OF CASES	PER CENT
Schizophrenia	10	45.4
Emotional instability	12	54.5
Total	22	100

TABLE VII. ORGANIC GYNECIC PAIN, 511 CASES

		NO. OF CASES	PER CENT
1. Infection		411	80.4
a. Cervicitis	356		
b. Salpingo-oophoritis	42		
c. Endometritis	13		
2. Endometriosis		67	13.1
3. Ectopic pregnancy		24	4.69
4. Uterine myoma		6	1.17
5. Twisted ovarian cyst		3	.587
Total		511	100

TABLE VIII. NONORGANIC GYNECIC PAIN, 289 CASES

	NO. OF CASES	PER CENT
1. Dysmenorrhea	143	49.4
2. Follicle rupture or bleeding	131	45.3
3. Pelvic congestion	15	5.19
Total	289	100

In the 800 cases of pelvic pain of gynecic origin it was necessary to perform surgery of a major character in 85 cases, or 10.6 per cent. Of these 85 instances, 32, or 37.6 per cent, were done for what were thought to be acute emergencies as follows: twisted ovarian cyst 3, ectopic pregnancy 24, and ruptured follicle with bleeding 5. In the other 53 cases, or 62.4 per cent, surgery of a major nature was performed only after exhaustive observation and surveys had determined that the procedure would be of benefit to the patient. These included 3 instances of myomas of the uterus, 10 cases of presacral neurectomy for dysmenorrhea, 25 operations for endometriosis, and 15 for pelvic infection.

Minor surgery for correction of cervicitis was performed in 236 instances as cold knife biopsies and conizations.

In 22 instances appendectomies were performed for a diagnosis of acute appendicitis.

Comment

We do not think it appropriate to lengthen this publication with a discussion of each of these entities. Rather we would like to encourage the clinician to refresh himself with the various signs and symptoms of these entities listed in the tables in the light of the basic anatomy and physiology of pain in order to appreciate their origin. Then and only then, can he effectively seek out the etiology of such complaints.

We do think it most appropriate to call the attention of the clinician, first, to the fact that 571, or 41.6 per cent of the women in this series, had pain which

could be adequately explained as arising from organs other than the uterus, tubes, ovaries, and their appendages; second that of the 800 women, or 58.4 per cent, in whom pain was explained as being caused by organic disease or nonorganic functional states of the female reproductive organs, only 85 patients, or 10.6 per cent, needed major surgery for therapeutic relief of their complaints.

If an acute state is not noted on initial history and examination, we feel that exhaustive clinical observation, surveys, conservative measures, and reexamination should be conducted prior to submitting any woman to major surgery of the reproductive organs for relief of pain.

Conclusions

1. A review of the basic anatomy and physiology concerned with gynecic pain and pain which simulates it is presented.

2. A series of 1,371 women admitted for a complaint of pain thought to be gynecic in origin is reviewed.

3. Five hundred seventy-one, or 41.6 per cent, of these women actually had pelvic pain of other than gynecic origin, and 800, or 58.4 per cent, had gynecic states to explain the origin of their pain.

4. Only 10.6 per cent of these women required major surgery for relief of pain.

5. It is recommended that, unless an acute state requires it, surgery can be deferred until a definite etiology of the complaint of pain can be determined.

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Discussion

DR. GERALD I. MILLER, Kansas City, Mo.—Pain, an often bizarre and diagnostically elusive gynecologic symptom, has been the target of a number of worth-while papers presented before this society in past years. However, I feel that those of us who have heard our honored guest's paper yesterday and the present essay have attended a truly noteworthy panel on the subject of pelvic pain.

The authors' recapitulation of the physiology of pain and the neuroanatomy of the pelvis is both lucid and timely and, I believe, deserves the careful perusal of most of us.

I find it difficult to dispute or to criticize the clinical breakdown of the cases of these obviously careful clinicians. It would be illuminating, however, to know the incidence of alleviated pain in some of their major operative cases. We have lost much of our enthusiasm for presacral neurectomy, and, since only slightly more than one-third of the reported cases of endometriosis were operated upon, I wonder if conservative procedures were done and, if so, whether the authors were content with their results? I believe the incidence of major operative intervention might still conservatively be lowered.

I am not aware that the diseased cervix is commonly a source of pain, though I note 356 cases of cervicitis producing gynecic pain, of which 235 received minor surgical treatment. It would be helpful to note again the incidence of alleviation of pain in this group. I concur in the attitude that the cervix is capable of producing symptoms other than discharge and bleeding, but I have a strong feeling that the organ is most often a source of pain when associated with co-existing disease, namely, parametritis, peritonitis, and pelvic congestion.

Finally, it is my feeling that gynecology is on the threshold of a new era. We have passed through the era of infection, of the pessary, and of surgery for the supposedly malpositioned uterus. It is true, we will never be without the problems of infection, neoplasm, endometriosis, or the conjecture produced by symptoms arising from the skeletal, genitourinary, and gastrointestinal systems. However, the physical and emotional stress and longevity of today's society results in symptoms of pain arising from anxiety and poor adaptation. Borderline neuroses with altered threshold of pain result in vague symptoms, either singularly or camouflaged by insignificant or minor pathologic states. We believe that a high percentage of gynecic pain, after careful exclusion of organic pathology, must be categorized as functional and in this group of patients a high incidence of psychosomatic overlay is observed. Obviously, then, we must increase our interest in the physiology of the autonomic nervous system, vascular, and endocrine systems, and selective extracellular fluid balance (i.e., pelvic edema), for new answers to the problem of pelvic pain.

At the risk of seeming facetious I must say I am appalled at the stability of Texans. The authors record only 22 patients out of the entire group as psychiatric, 10 of which were schizophrenic and 12 emotionally unstable. These conceivably should be managed by the psychiatrist. Because I feel that borderline psychiatric states, namely, stress, anxiety, emotional immaturity, and poor adjustment, play an important role in functional pain, I believe they should be included in such a survey and I must say our problem in Missouri in this regard is serious.

If the author's statistics in this regard are accurate—then I say, "Thank God for Texas," an isolated citadel of strength and stability among the fearful, fretful communities in this civilization of the atomic age.

DR. HOWARD C. TAYLOR, New York, N. Y.—It seems to me that the topic that has just been discussed is very similar to the one we talked about yesterday, and it is perfectly natural and proper that in a field we do not understand one group should be interested mostly in vascular changes and another group should be putting their principal attention on the autonomic nervous system, perhaps with its sensory components. Both factors I think are present, and there is no source of argument in deciding which at present is the more important.

I want to speak principally on the part of the paper that apparently was not read, namely, that concerned with the field of surgery in this area, which Dr. Miller hinted at.

Before doing that, I have three brief comments:

First, if I understood Dr. Guerriero's diagram of the autonomic nervous system of the pelvis, I believe he indicated that there were afferent fibers accompanying the pelvic nerves, the nervi erigentes, as well as the sympathetic nerves in the hypogastric plexus.

If that is true—and I think there is some evidence for it—then there is a fairly good explanation of why all pelvic visceral pain is not relieved by the resection of the

presacral nerve of the hypogastric plexus, because some of the afferent impulses do not go through this nerve but go backward through the deeper parts of the pelvis and are quite unreached by this operation.

The anatomy and physiology of the pelvic autonomic system are certainly not yet fixed, and perhaps in the discussion Dr. Guerriero would comment on whether the evidence is good that afferent fibers do go posteriorly through this parasympathetic nerve.

Second, I would like to comment briefly on the difference of opinion apparently existing between us as to the use of the word "psychosomatic." If I understood Dr. Guerriero correctly, he thinks it more proper to regard these nonorganic pains as essentially gynecic, with a psychiatric overlay. The difference between that and regarding these pains as largely emotional with a gynecic underlay is certainly too trivial to argue about, so I think we here really would be arguing about words.

Yesterday I indicated that 15 out of 100 cases that I reported had been operated on, and one or two people said to me that this was a high operative rate on a nonorganic condition. This, I think, is true. I am glad to have the opportunity to explain this to some extent.

First of all, these were not all of the cases of pelvic pain that were seen during this period. They were, in fact, all private cases. They were not all my private patients who had pain, either, but they represented a selected group, many of them referred because of previous failures, and they represented also cases selected as most definitely having this condition.

I said, as I remember, that this was not statistics—it was description—and the incidence of symptoms was based on the group of most severe cases that I could find in that five-year period. So, this is not a statistical proportion that was operated on.

Aside from that, I think I said that I thought one of the cornerstones of the treatment of this condition was the patient's reproductive program. This perhaps is a somewhat unconventional approach to it. I think these people should be told that this whole business may interfere with their reproductive plans.

This condition certainly is of very long standing. It is difficult to cure. It is advisable that they should get their families finished, and that defers the operation five to ten years. This policy was regularly followed.

I said also that no patient should be operated upon unless the pain had been persistent for many years—and I mean two, three, four, five, and sometimes, in my series, ten years.

Third, it should not be resorted to unless every other method had been tried, and under this heading I include psychiatric advice. Within the last few months we have started a pain clinic in our outpatient department. The patients of this type see a psychiatrist who has a psychologist with him to do a certain number of psychological tests, and we propose in the future that none of these patients will be operated on unless they are not only gynecologic failures but also psychiatric failures.

On the other hand, if a patient has had pain for ten years, if she has three children, if she is approaching 40, and if all other methods of treatment have failed—and these cases are very few in number—then I see no reason for sentimentally refusing operation, even if what goes to the laboratory looks relatively normal. I think a consultation before an operation is much more important than censure afterward.

DR. GUERRIERO (Closing).—I do not think there is any difference of opinion between the two discussants. We feel exactly as do the other two. The only difference, as Dr. Taylor said, probably is a matter of wording. However, we are concerned with the fact that there are a certain number of women who, over a long period of time, as Dr. Taylor mentioned, will have pain and pain and pain, and get no result from any form of treatment one could think of; and in that group of women there may be minor gynecologic disorders such as cervicitis, which Dr. Miller mentioned.

We think that oftentimes operative procedures for clearing up minor or associated major gynecologic entities, along with psychosomatic disturbances, will eliminate that

individual's pain. That was the reason why in the physiology we tried to stress that women can have minor pelvic visceral disturbances which will produce no pain, and that when you add to that subthreshold stimulus, other violent emotional stimuli, then that pain becomes noticed by the sensory portion of the higher centers, and the patient then becomes conscious of it.

In the gynecic pain series infection leads the list with endometriosis, ectopic pregnancies, the uterine myoma which actually had degenerative or infective changes, and twisted ovarian cyst following, totaling 511 cases. The highest incidence was that of cervicitis, which Dr. Miller objected to. We still feel that the woman who has cervicitis is going to have some parametritis and some pelvic pain, and that the eradication of that cervicitis will eliminate, in most instances, her gynecic pain, because it removes one of the components of stimulation to the higher centers.

We divide gynecic pain into nonorganic cases—dysmenorrhea, follicle rupture, or bleeding—and pelvic congestion, which Dr. Taylor mentioned.

Surgery was done as an emergency measure in 32 instances, and delayed surgery was done in 53 cases.

Three-fourths of the emergency operations were for ectopic pregnancies, which no one can disagree with; for twisted ovarian cyst in 3 cases, and for ruptured bleeding follicles in 5 cases.

The delayed surgery was for endometriosis, pelvic infection, and dysmenorrhea, and myomas. Actually the cases of dysmenorrhea included the pelvic-congestion series.

Now, to answer Dr. Taylor's remarks about the autonomic nervous system: It is a known fact that we are just on the threshold of understanding the sensory innervation in the pelvic viscera. The person who does a so-called sympathectomy with the idea that he is going to eliminate all pain from the pelvis is under an illusion. It is anatomically impossible, unless he wishes to clean out the entire posterior area of the pelvis, to do a thorough presacral neurectomy. However, one can do enough neurectomy to lower the patient's threshold of reception of pain and give that individual some relief from her pain.

It is impossible to eliminate the parasympathetic autonomic system, because once that pelvic plexus in the deep areas of the pelvis is interrupted, or if you interrupt it higher, interference with bladder and bowel function will occur.

IN VIVO STUDIES WITH DIRECT SKY BLUE* OF THE LYMPHATIC DRAINAGE OF THE INTERNAL GENITALS OF WOMEN†

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THE embryologic development of the human female internal genitals is rather well understood. The anatomy, including the blood vessels, is adequately described in many texts, and Anson[2] gives an excellent description of the variations in the hypogastric basin. Lymphatic drainage is not so well known. The usual description of the ovarian lymphatics is that they "follow the ovarian vessels." Cade[3] mentions a communication between the two ovaries over the dome of the fundus. He also mentions the nodes involved in uterine drainage, but leaves the channels in doubt. Ackerman and Regato[1] describe three routes from the cervix, and three from the endometrium. One of these is common to both. This is the "preureteral" or principal chain which follows the direction of the uterine artery in front of the ureter, and ends in the middle and internal nodes of the external iliac chain. The second cervical route is "retroureteral" and follows the uterine veins to the hypogastric area. The third is least constant. It is the posterior pedicle which parallels the rectum to the laterosacral nodes, and eventually to the sacral promontory. The two additional paths of uterine drainage traverse the round ligament (infrequent) to the inguinal area, and the uteroovarian ligament (most common) to the preaortic nodes, using the precaval (right) and lateroaortic (left) chains. It is the involvement of the uteroovarian ligament which accounts for the spread of endometrial cancer to the ovary.

In 1923 Leveuf and Godard[6] described the uterine lymphatics, and this later led them[7] to try the surgical removal of the "principal" lymph nodes in the treatment of cervical cancer. At approximately the same time Taussig[8] first reported his technique of pelvic lymphadenectomy in carcinoma therapy. He[9] later reported the order of frequency of nodal involvement as hypogastric, obturator, ureteral, and external iliac. Most of his patients had received preoperative radiation of variable intensity. Way[10] believes that the paracervical or ureteral node is a misnomer. Usually, it is nothing more than a fusiform swelling at the junction of several large lymphatic trunks. He also states that perineural lymphatics in many situations form a route for spread, but believes that the primary involvement is in the "interiliac" nodes, most of which are in the external iliac chain.

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*These studies were aided by Wyeth Laboratories, Inc., who supplied liberal quantities of Wydase and Direct Sky Blue. Direct Sky Blue differs from Pontamine Sky Blue, originally furnished in powder form by E. I. du Pont de Nemours & Co., Inc., in the location of the sulfonic radicles in the naphthol nucleus at positions 5,7 instead of 3,6. Direct Sky Blue is a true solute, and therefore has no particulate size.

†Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

Reporting primarily on autopsy material, Henriksen[5] offers evidence that radiation modifies lymphatic spread, reducing parametrial invasion from 77 to 33 per cent, whereas hypogastric and obturator involvement almost doubled. External iliac disease increased one and one-half fold. However, "distant" pelvic metastases were not influenced by treatment. In a footnote he mentions that Pontamine Sky Blue was given prior to laparotomy, and this permitted localization of the nodes, and easy tracing of the lymph channels.

The injection of dilute India ink into the cervix at three and nine o'clock was reported by Zeit and Wilcoxon,[13] who noted occasional spread of the carbon across the midline. The obturator, hypogastric, and lower iliac nodes were stained a light gray as early as four hours later. Zeit[14] has also experimented with injections of radioactive material (Au^{198}, P^{32}, and Sr^{90}) into the cervices of dogs. Results were inconstant and unsatisfactory for proper interpretation.

Weinberg and his associates[11, 12] have written extensively on the safety of Pontamine Sky Blue, and have reported its use in the identification of nodes at operation for bronchiogenic and gastric cancer. In our previous report[4] we reviewed these and other publications which led us first to the use of Pontamine Sky Blue, and then to Direct Sky Blue in the study of ovarian lymphatics. This work has now been extended to the cervix and endometrium, all of which are included in this report. We modified Weinberg's technique by injecting 50 turbidity reducing units of Wydase through a fine needle into the ovarian hilum, and followed through the same needle with 1 ml. of 4 per cent aqueous solution of Direct Sky Blue. The injection was given very slowly, taking one and one-half to two minutes for its completion. Twenty-eight patients were studied; 5 were controls. In the rest various combinations of ovarian ligaments were ligated, and the variations in dye dispersal studied.*

Cervical injection in a few patients was also done at the time of the preoperative vaginal preparation. This did not permit adequate delineation of the cervical lymphatics. In 23 additional patients injection was made into the fibromuscular portion of the cervix at its junction with the vaginal fornix. A 22 gauge spinal needle replaced the hypodermic needle used in injecting the ovary. Injections were made without anesthesia twelve to eighteen hours before the scheduled laparotomy. Mild and dull cramps were experienced by most patients after intracervical injection. This almost never occurred if the injection was paracervical. In only one subject did the cramps last longer than ten minutes. Modifications in the amounts of Wydase injected had no effect on the cramps. Each patient was permitted to sit up and return to her room immediately after the injection was completed. In one patient a cervical stump was injected, and in another the stalk of a prolapsed, pedunculated submucous fibromyoma was injected. Both of these were done on the operating table under anesthesia. Two patients were pregnant, one each in the cervical and ovarian groups. There was no modification in the direction of the spread, but the dispersal was more rapid.

*Shading in illustrations shows extent of dye spread, arrows show direction of spread.

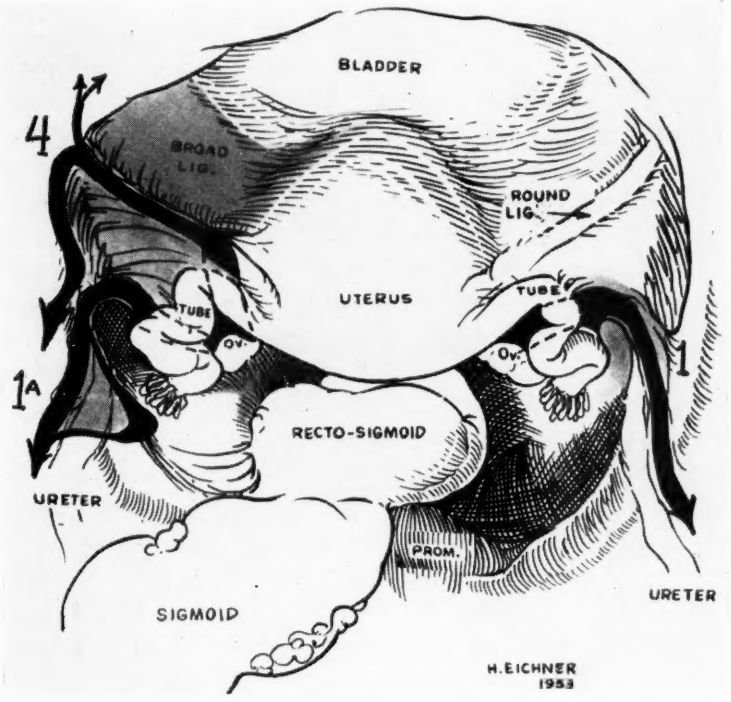

Fig. 1.—Anterior view of ovarian drainage. *1* shows control spread of right ovary and *1A* of left ovary. *4* shows round ligament spread.

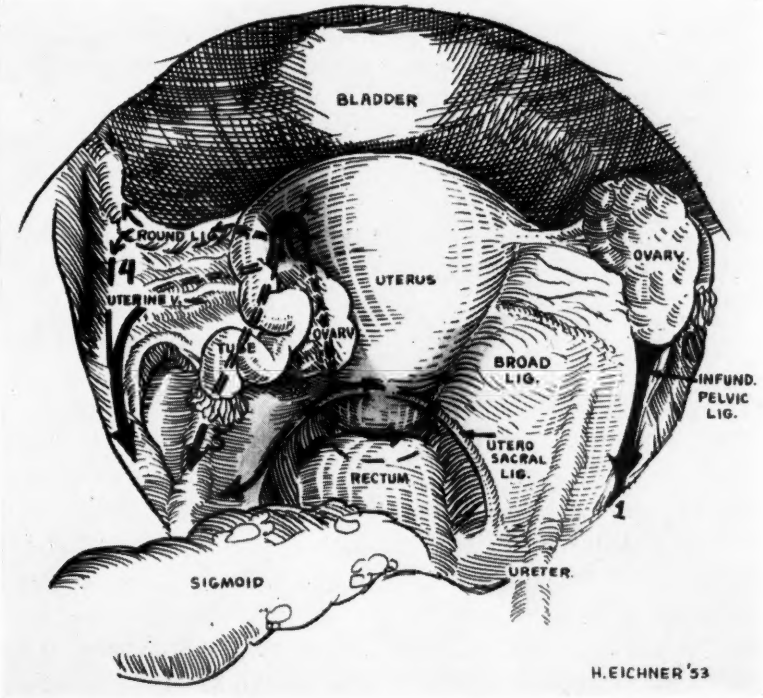

Fig. 2.—Posterior view of ovarian drainage. *1* and *4* are as in Fig. 1. *2* shows utero-ovarian ligament spread descending the posterolateral aspect of the uterus to the uterosacral ligaments where the spread encircles the rectum and crosses the midline. Spread continues laterally to the hypogastric region. *3* shows the direction of deep spread along the course of the ureter toward the hypogastric area.

We noted again in the cervical series our previous observation that the spread of dye was influenced by the state of ovarian function, being least rapid in the castrate. Since we had learned by experience that artifacts in dye spread could be produced surgically, and that these errors influenced the results and their interpretation, only patients with "clean" pelves were used in the latter portion of this study. Tubal lymphatics were not investigated since both uterine and ovarian spread frequently involved tubal drainage areas. In no patient were we able to force dye from the ovary, tube, cervix, uterine serosa or muscularis into the endometrium. Uterine drainage was always away from the cavity. Except for this, we did modify the spread of dye by blocking "normal" channels. There apparently was some change in the dye during the period of experimentation as the dye washed out of the early specimens during formalin fixation, but did not do so in some of the later ones. This factor might be related to the amounts of Wydase used.

In general, unblocked ovarian lymphatics follow the course of the ovarian vessels (*1* in Figs. 1 and 2). In our "left" control patients some dye always reached the hypogastric nodes (*1A* in Fig. 1). After ligation of the infundibulopelvic ligament, dye spread mesially to the uterine serosa, descended the corresponding posterolateral peritoneum (*2* in Fig. 2), and reached the deep pelvis, the hypogastric nodes, and even the sigmoid mesentery through the uterosacral ligaments and the cul-de-sac peritoneum (Fig. 2). By means of these ligaments and the peritoneal reflection of the rectosigmoid dye crossed the midline (Fig. 3). When the uteroovarian ligament also was ligated, some dye entered the deeper portions of the broad ligament to follow the course of the ureter to the pelvic brim (*3* in Fig. 2). Most of the dye advanced to the lateral pelvic wall by way of the round ligament (*4* in Figs. 1 and 2). A small amount entered the inguinal canal, but none was ever seen in the groin. The greater portion of the dye went cephalad along the external iliac chain. When dye was forced into the deeper portions of the broad ligament, the obturator nodes were always stained.

A pattern was established in the response of the cervix to injection, but the specific staining in any individual case could not be foretold. We varied the technique, using 0 to 50 units of Wydase, 1 to 2 ml. of Direct Sky Blue, and made injections into various portions of the cervix and paracervical tissues. In general, one hour was inadequate for the detection of spread. We did not try injections at two, four, or six hours. An interval of twelve to eighteen hours was most satisfactory. Almost invariably the right half of the cervix was the site of injection. Dye never crossed the midline anteriorly unless it was injected at twelve o'clock. Regardless of the site of injection, dye crossed the midline posteriorly if adequate time was allotted. This occurred earliest in injections at six to nine, and latest in those at nine to twelve o'clock. Anterior injections rapidly stained the vesicouterine fold of peritoneum, and then spread to the lateral pelvic wall in a widening band (Fig. 4). The posterior injections appeared first at the uterosacral ligaments and proceeded anteriorly and laterally toward the ovary. At the level of the uterine vessels dye traversed the posterior broad ligament to the hypogastric nodes, and to the obturator area (Figs. 5 and 6) if time permitted.

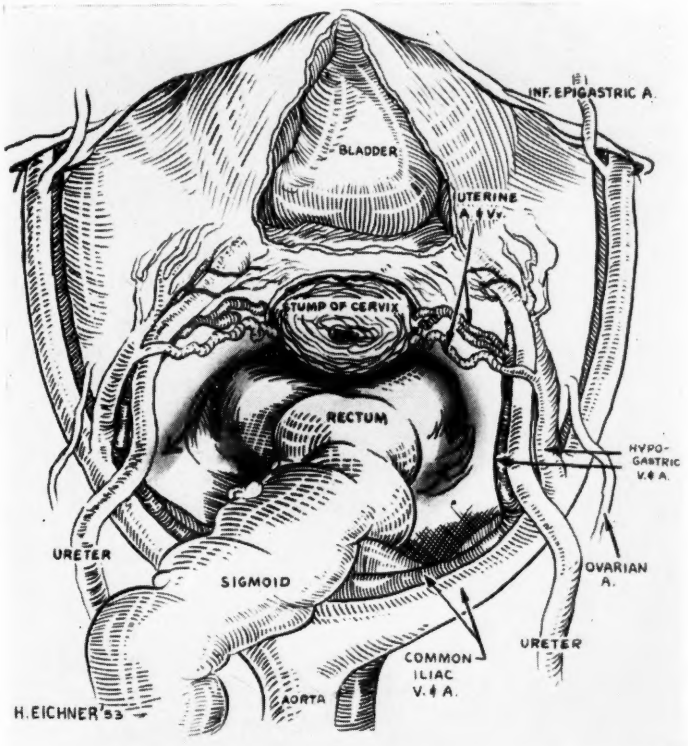

Fig. 3.—Deep pelvic view of ovarian drainage. This demonstrates the path taken in crossing the midline in the uterosacral region and at the peritoneal reflection of the rectosigmoid.

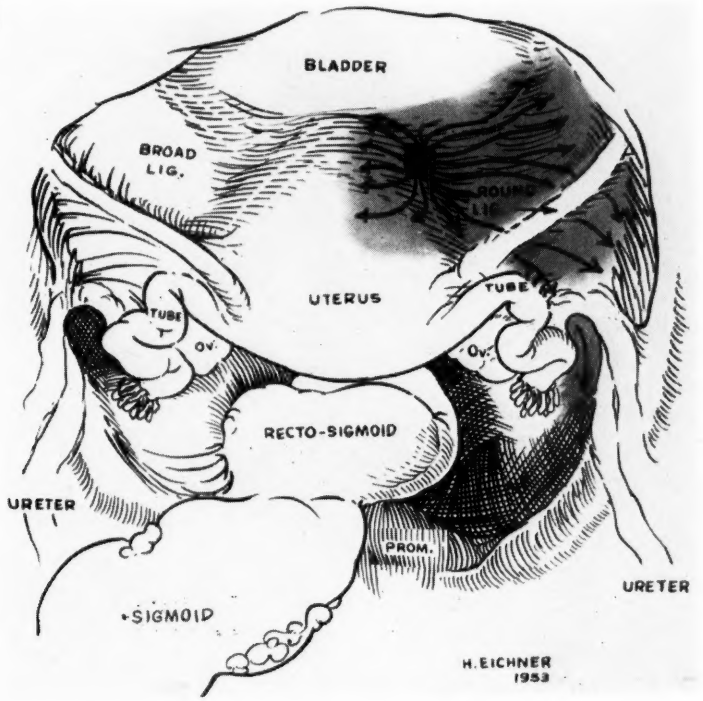

Fig. 4.—Anterior view of cervical drainage. Note that spread reaches but does not pass the midline, and that the tube, round ligament, and infundibulopelvic ligament are not stained. The dye, however, has reached the hypogastric area.

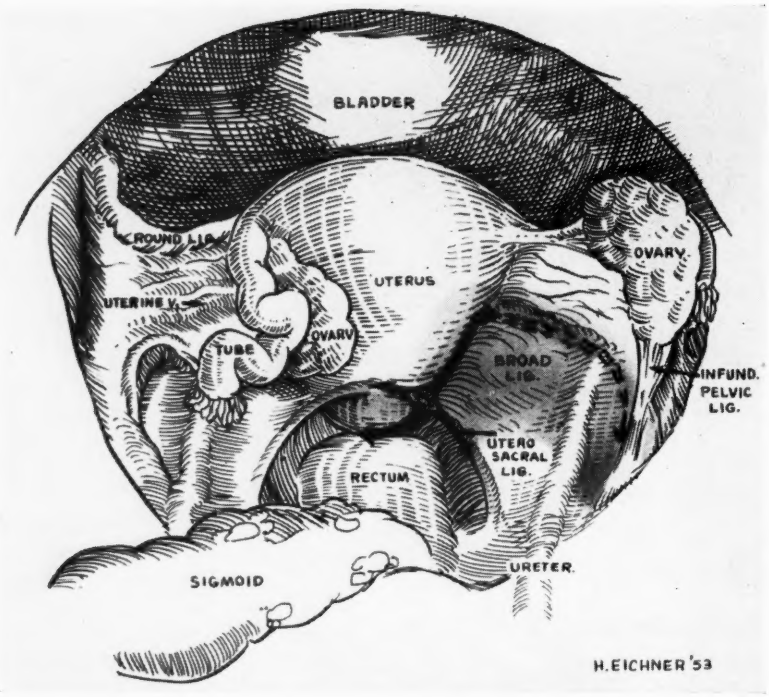

Fig. 5.—Posterior view of cervical drainage. Dye spread crosses the midline posteriorly and follows the uterosacral ligament toward the sacrum. It also spreads through the deeper layers of the broad ligament to the hypogastric area, but does not involve the ovary,* upper broad ligament, or infundibulopelvic ligament. The ureter is not stained beyond its emergence from the broad ligament.

*In one patient the ovary took up the dye from a cervical injection. The pathway could not be determined.

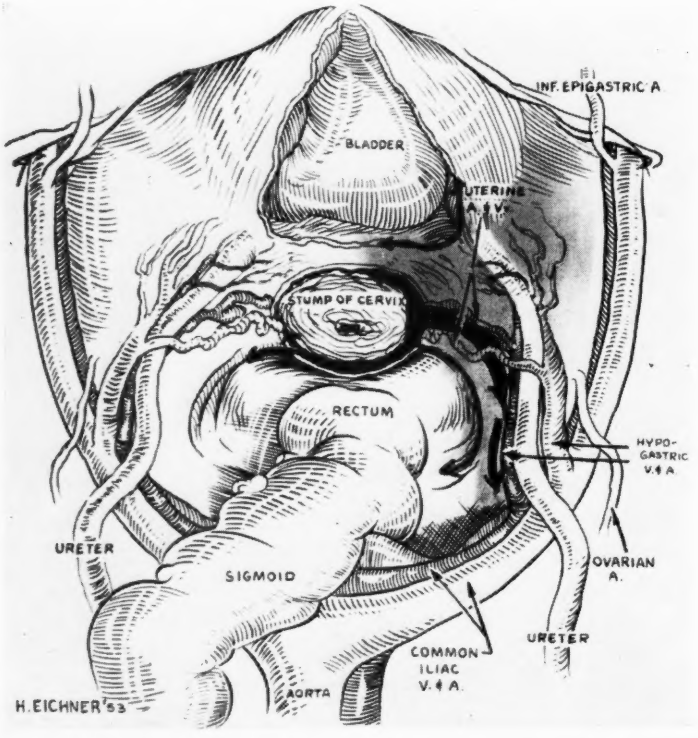

Fig. 6.—Deep pelvic cross-sectional view of cervical drainage. This demonstrates the dye crossing the midline posteriorly, but not anteriorly. The dye spread to the lateral pelvic wall in the deeper portions of the broad ligament, usually through the retroureteral channels. Invariably the hypogastric nodes were reached before any spread occurred toward the obturators. In this series we could not produce external iliac spread.

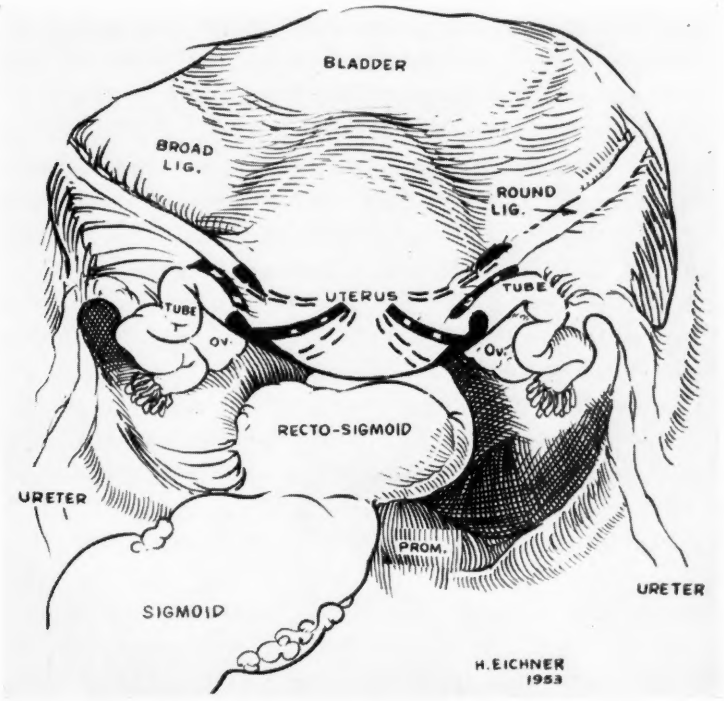

Fig. 7.—Anterior view of corpus or endometrial spread. Only the cornua are involved. There was only one patient in this portion of the study.

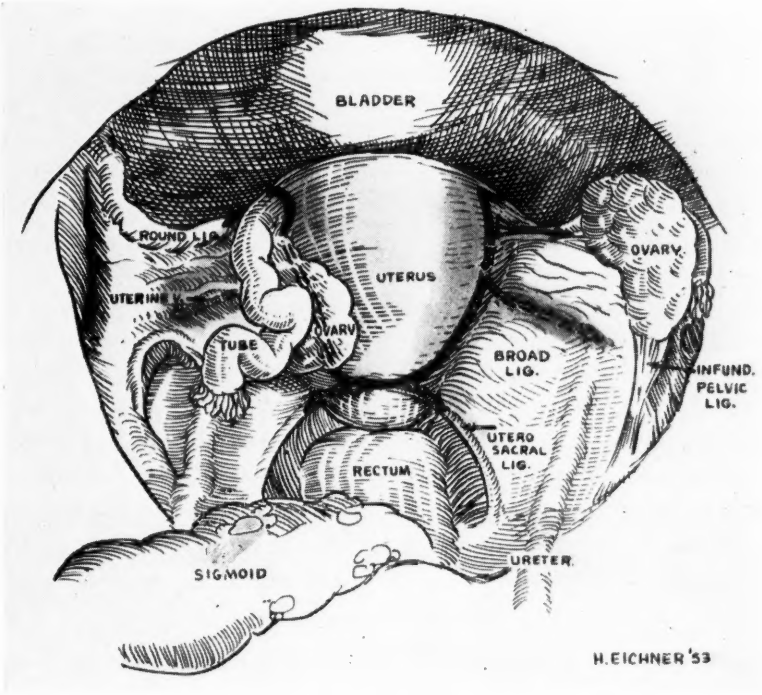

Fig. 8.—Posterior view of corpus or endometrial spread. Spread was bilateral to the utero-ovarian ligaments and down the posterolateral aspects of the uterus. Small amounts spread subserosally across the entire posterior fundus, and followed the uterine vessels toward the lateral pelvic wall. A larger portion of the dye pooled in the uterosacral area, and then traveled pathways similar to ovarian and cervical spread across the midline and into the deeper portions of the pelvis.

At no time did we see the "interiliac" or the middle and internal nodes of the external iliac chain stained by cervical injections. Regardless of the injection site, the deeper portions of the broad ligament were stained most deeply. The ureter was never stained beyond its emergence from the uterine pedicle (Fig. 6). These findings suggest that the retroureteral chains are most frequently involved, and that possibly the preureteral chain is not involved until the posterior ones are blocked, at least partially. When the broad ligament was opened, the obturator area was stained after and apparently from the hypogastric area. We were never able routinely to stain the external iliac nodes, and are still studying this problem. In no case was the myometrium or the muscularis of the bladder dyed. In only one patient was the ovary stained. At laparotomy there was no visible link between the deeply stained base of the broad ligament and the blue-stained liquor of the ovarian follicles. The rest of the ovary was not involved. The ovary was not removed for study. The uterus had been retroverted, with the ovary lying behind it in the cul-de-sac. The cervical stump of an aged castrate was injected just prior to laparotomy for incomplete intestinal obstruction. Despite extensive pelvic dissection no dye was visualized in the abdomen. It was later found in the rectovaginal septum when the stump was removed vaginally. The dye had begun lateral and caudal spread, and was seen along the pudendal vessels when Alcock's canal was opened in extending a Schuchardt incision. The perineum was never visibly stained. The patient was a Negro.

Since we were unable to produce centripetal uterine staining, we tried submucosal injections at or near the internal os. Drainage was immediately peripheral, and identical with that of the cervix. When the site of injection could be located at hysterectomy it was discovered that no injection had been made intramyometrially. In the patient with the prolapsed fibroid, 20 units of Wydase followed by 1 ml. Direct Sky Blue were injected into the stalk. The protruding tumor was then amputated, and a repair was done. Section of the stalk shows an unstained central core, evidence of centrifugal flow. At laparotomy both uteroovarian ligaments and cornu were stained (Fig. 7). The remainder of the dye followed the ovarian pathway subperitoneally down the posterolateral portion of the corpus, crossing the midline at the insertion of the uterosacral ligaments, and started a descent of these ligaments (Fig. 8). However, in differing from ovarian type spread, the entire posterior fundal peritoneum was stained lightly blue, possibly because the tumor had a midline insertion. Frozen sections of formalin-fixed fundal tissue disclosed that the dye had passed through the uterine wall between the muscle bundles, primarily in the adventitia of vessels. The intima was lightly stained, the media unstained. No dye was seen on the anterior uterine surface below the cornu.

Summary

Modifying the technique of Weinberg and his associates with Direct Sky Blue, the lymphatic drainage of the human cervix, endometrium, and ovaries was studied at operation. Dye dispersal was noted, and frequently photo-

graphed. Composite line drawings of these photographs are presented. All unobstructed lymphatic drainage is centrifugal. Ovarian drainage usually follows the ovarian vessels, but will go mesially, even across the midline, via the posterolateral uterine peritoneum and the uterosacral ligaments, if primary pathways are blocked. The round ligaments and the periureteral channels apparently are not patent unless the uteroovarian and infundibulopelvic ligaments are both obstructed. We could not drive dye into the endometrium. However, endometrial drainage went almost immediately to the uteroovarian ligaments, and then proceeded down the posterior peritoneum to the uterosacrals. This dye also crossed the midline at this point. Results of cervical injection were inconstant, but the posterior drainage paths to the hypogastric area seemed to be preferred. The uterosacrals were always involved, and the dye always crossed the midline posteriorly, never anteriorly. The fundus uteri and the bladder were never stained. We were unable to stain the external iliac nodes by cervical injection.

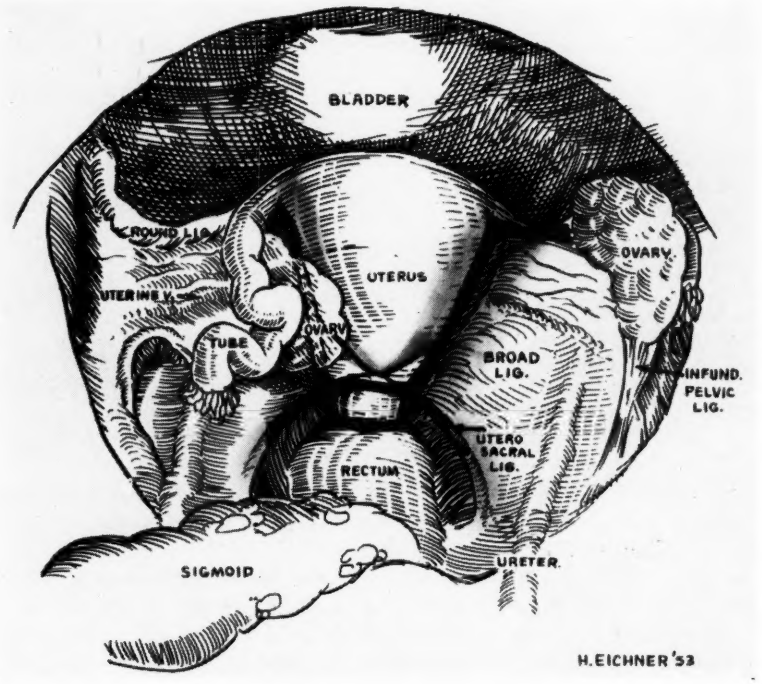

Fig. 9.—Common drainage pathways for the cervix uteri, corpus uteri, and the ovary. These demonstrate the importance of the uterosacral ligaments and the cul-de-sac peritoneum, as well as the posteromesial aspects of the broad ligament and the lateral aspects of the uterus in the spread of benign and malignant gynecic disease.

Conclusions

1. Direct Sky Blue as used in this experiment was innocuous to the patients even though large amounts of stained tissues were not removed.

2. The method described is adequate for the study of regional lymphatics, but is not yet developed for the best delineation of the cervical nodes. This

may be because of the great distance from the organ to its target nodes. We have not yet determined whether the increased dye dispersal secondary to the use of Wydase is clinically helpful in the case of the cervical nodes.

3. For adequate evaluation of these problems, patients with "clean" pelves must be used, as any excessive manipulation or dissection will increase the spread of the dye, and may produce technical artifacts. We are continuing our study.

4. Greater consideration must be given the uterosacral ligaments in the spread of pelvic disease or tumor. These ligaments with the posterolateral uterine peritoneum and the base of the broad ligament form the anastomosing channels for ovarian, endometrial, and cervical drainage, and are a major part of the pathway of extension of disease across the midline (Fig. 9).

I wish to express my appreciation to Mr. Robert Newhouse, assistant photographer at Mt. Sinai Hospital, for his splendid cooperation, and to my brother, Henry, for the anatomical drawings.

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Discussion

DR. E. G. HOLMSTROM, Salt Lake City, Utah.—I have learned that intimate knowledge of a subject is not a prerequisite to discussing it. The authors' observations have been helpful in supplying some of the missing links in our knowledge of lymphatic drainage of the internal genitals. The practical implications of the observations, particularly in regard to the management of malignant disease, are evident. As far as I can judge at this time, the findings do not indicate that there should be any radical change in our present concepts of the proper management of malignant disease of the female genitals. The observation that the external iliac nodes did not contain dye after injection of the cervix might, at first glance, appear to be contrary to the observations of others who found tumor spread to these nodes in about one-fourth of patients with untreated carcinoma of the cervix. The time interval here may be the reason for the discrepancy of findings. Observations at longer time intervals following injection of the dye would probably settle this point.

Basic studies such as these presented here today are essential prerequisites to a wider use of radioactive materials in the treatment of malignant disease.

DR. EICHNER (Closing).—First of all, in regard to radioactive materials, work has been done and is being done in several places with gold^{198}, cobalt^{60}, strontium^{90}, and

several of the other types, in an attempt to localize these nodes. Practically all observers have noted that it is impossible to get dye of any sort or any of the radioactive materials routinely into the external iliac nodes. It can be done irregularly in various patients, but no one can tell ahead of time in which patient it will be successful.

We hope to be able to report next year on further studies along this line, as we are at the present time injecting all entrances into the pelvis—the femoral canal, the inguinal canal, the sciatic notch, and several other places—in animals as well as in human material.

Our work has demonstrated that for practical purposes the hypogastric nodes are the first hit, and we disagree somewhat with the Ackerman and Regato studies which show that carcinoma goes elsewhere. Of course we are not dealing with carcinoma—we are dealing with a substance which does not have a definite size.

The dye is a true solute and it spreads as a solution rather than a cellular debris. Our material goes to the hypogastric nodes first, and in those cases in which the obturator area has been involved we have seen the involvement occur secondarily from the hypogastric area and not directly. We have opened up the broad ligament in a number of cases and have watched the dye spread slowly from the hypogastric area into the obturator area. We have been able to push it into the external iliacs, but we have not seen it go there of its own accord.

Recently, in a group of dogs in which the inguinal and femoral canals were injected, one hour later dye was not visualized in the pelvis. However, a week later, when the abdomen had not been reopened, there was dye spread to the inferior epigastrics along the abdominal wall as well as into the superficial femoral vessels and the mesial aspects of the thigh.

MATERNAL DEATH STUDIES—DO THEY HAVE PRACTICAL VALUE?*

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DURING recent years surveys of maternal deaths have increased in number and in scope. At present some twenty are conducted on a statewide basis. These deaths occur in women who should have no particular or unusual liabilities. They are preponderantly preventable.

Two years ago, in his presidential address before this association, the late Russell J. Moe outlined values which could result from studies of maternal deaths. Well-conducted surveys, he pointed out, uncover actual factors contributing to these fatalities and teach many lessons. It was his conviction that the lessons could be turned to educational purposes and thereby could become a further factor in reducing maternal death dates.

We are in hearty accord with this point of view. The purpose of this report is to argue that maternal mortality surveys will have more practical value if they are aligned with current legislative and educational trends. To support this argument we wish to review briefly the conduct and certain findings of the Michigan maternal death study, to indicate how the lessons learned are being utilized, and to suggest additional ways in which the study may be made more effective in decreasing maternal deaths.

The inadequacy of any study of maternal deaths based upon death certificates has been emphasized repeatedly. It is evident that, if the studies are to have any value, the data relating to the individual cases must be complete and accurate.

The study in Michigan is made by the State Medical Society through its maternal welfare committee in cooperation with the State Department of Health. Costs of the study are shared by both. The state is divided into ten areas to each of which a certified obstetrician-gynecologist is assigned as an investigator. He is notified as soon as a maternal death is reported. Each case is studied personally by him and includes a review of the hospital records, pathology protocols, and other pertinent documents. Interviews are had with the attending physician, the consultants, hospital personnel and, on occasion, with relatives or others who may have significant information. From these data a detailed form is filled out for further study. In addition, the investigator prepares a summary of the factual data and includes comment upon the adequacy of hospital facilities and the completeness of the medical records.

The completed report is analyzed by a subcommittee which judges whether the death was due to obstetrical or nonrelated causes and whether it should be

*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

considered preventable or nonpreventable. For preventable deaths, responsibility is assigned to the patient, the physician, the consultant, the hospital, or to any combination. Whenever possible, the factors involved also are determined. At the end of each year the completed cases are given to another subcommittee for final classification and incorporation in the formal reports of the committee. All data and comment must be reviewed and approved by the Council of the Michigan State Medical Society before they may be released for general publication. County societies conducting studies of maternal deaths in their own localities are furnished with a copy of the investigator's original report for independent analysis and action.

The Michigan study became statewide in 1950. The principal causes of death as found in our study do not differ from those reported from other states. Percentage incidence is strikingly similar. Variations result from the absence of uniform standards of classification. They reflect the difficulties involved in attempting to determine the principal factor in equations filled with multiple unknowns. A comparison of our findings with those of Minnesota and Illinois (excluding Cook County) is presented (Table I) because these states are within the confines of this organization and because the general and professional populations are similar. No evaluation of the studies themselves is intended.

TABLE I

	MICHIGAN	MINNESOTA	ILLINOIS
Period of survey	1950	1950	1948-1951
Total deaths	92	46	297
Mortality rate	0.6	0.6	0.71
Hemorrhage	40.5%	19.6%	33.7%
Toxemia	19.1%	28.3%	25.9%
Infection	14.5%	15.1%	12.9%
Heart disease	8.0%	8.7%	1.6%
Anesthesia	8.0%	8.7%	4.9%
Other obstetrical causes	8.0%	19.6%	21.0%
Preventable factors present	43.0%	32.4%	79.5%

Classification of causes of death and assessment of preventability are admittedly difficult. We suspect that in many instances they are inaccurate. Nevertheless, they have value in focusing attention upon the areas where obstetrical problems exist. The specific nature of the problems, we have found, can be detailed only after a critical study of the deaths themselves. It is important, for example, to discover that hemorrhage is the leading cause of death. Yet if we are to find effective answers to the problems which hemorrhage poses, we must know the actual circumstances under which such deaths occur. Certain details of this variety as found in our study are worthy of brief mention.

Deaths due to hemorrhage, in our cases, were most often associated with ectopic pregnancies, placenta previa, placental abruption, and lacerations of the uterus and vagina. The most common fault was inadequate blood replacement. This too little, too late replacement occurred because hemorrhage was not anticipated, because the amount of blood lost was grossly underestimated, and, in certain situations, because blood was not available in the hospital for transfusion.

In ruptured ectopic pregnancies, deaths due to hemorrhage were charged almost equally to the patient and the physician. More than half of these deaths involved women who first had medical care after rupture and extensive blood loss had taken place. Professional neglect or procrastination in performing pelvic examination was apparent in the remaining cases. This reluctance to examine a patient with vaginal bleeding on the grounds that such examination might complete an impending abortion delayed diagnosis until the disaster itself made it obvious.

Uterine atony was certified as the cause of death in a significant percentage of these cases. Careful analysis suggested, however, that the fatal hemorrhage was due, more probably, to traumatic rupture of the uterus or extensive tears of the vagina. Deaths from hemorrhage proved to be due to uterine rupture were found associated with version and extraction, difficult forceps deliveries, and oxytocic stimulation of the uterus. Version and extraction was particularly lethal. It was selected injudiciously, often in desperation, with insufficient blood at hand, and without adequate assistance.

Second in the list is toxemia. Eclampsia was the major contributing factor in these deaths. Our study showed that signs and symptoms of an impending obstetrical catastrophe had been present from one to four weeks before it occurred. Professional inadequacy was shown in the failure to appraise the danger signals properly and to treat them adequately. Surgical termination of the pregnancy in the unstabilized patient contributed importantly to these fatalities. Many hospital deficiencies were found related to these deaths. Few other obstetrical emergencies demand so much from hospital facilities. Successful treatment of this complication requires good nursing, competent anesthesia, available blood, and functioning x-ray and laboratory services.

Chemotherapy has demoted infection to the third major cause of maternal deaths. Criminal abortions were responsible for most of these. Medical care was delayed by the patient until she was practically moribund. Quite surprising was the frequency of deaths from pulmonary emboli. In many the source was found at autopsy to be in the pelvic organs. Antibiotics had been used; but in the very pernicious fashion of being ordered without the cause being investigated when the first elevated temperature was charted.

Particularly disconcerting were the deaths assigned to heart disease. Rheumatic heart disease with mitral stenosis was the most common lesion. The condition usually was found early. In the majority of cases there had been consultation. Too often, and for reasons not clear to us, the cardiologists confirmed or established the diagnosis but took no part in the management of the patient during pregnancy. Improper treatment of cardiac complications demonstrated professional ignorance of the effect pregnancy has upon the cardiovascular system.

Anesthetic deaths preponderantly followed conduction block forms of anesthesia. In two-thirds of these, improper dosage or administration appeared responsible. The failure to have competent anesthetists available should be charged to the hospital. However, the verdict cannot be escaped that, when

anesthesia is administered by other than trained anesthetists, it is the responsibility of the obstetrician to make certain that the agents used are proper, that they have reliable margins of safety, and that personnel are available to treat whatever complications may result.

At this point an iconoclastic "So what" is well in order. And justly so, because of the vagueness of the usual solutions proposed for these problems. "He ought to know better" and "There ought to be a law" are familiar lay answers for problems equally complex outside the field of medicine.

The value of socializing trends in legislation remains a matter of considerable debate. Yet most of us will admit that when legislation is properly conceived and fairly administered it can be of distinct benefit to the general public. Improvement in maternal and child health has resulted in part from the aid given state health departments by the federal government under the Shepard-Towner Act of 1923 and the Social Security Act of 1935. In 1951 the Michigan State Legislature (Act No. 231, P.A. 1951) authorized the commissioner of health to license maternity hospitals and to establish rules and regulations for their government. To ensure balance and perspective, the commissioner enlisted the cooperation of various medical organizations and interested individuals to study and submit recommendations for these rules and regulations. Those adopted established basic standards for the physical plant, equipment, patient care, records, and reports.

The rules and regulations in force in Michigan differ from those established by other health departments in the absence of specific restrictions on medical practice. The attending physician still is held responsible for the professional care given, a responsibility which cannot be assumed properly or effectively by any public health official. Comparison of maternal and infant death dates for similar communities fails to show that any advantage whatsoever can be claimed for rigid requirements regarding professional qualifications and practice (Table II).

TABLE II

1950	DETROIT	CHICAGO
Maternal death rate	0.6	0.6
Infant death rate	26.8	25.7
Live birth rate	28.4	21.8

We believe that an enlightened, conscientious, and cooperative profession has greater effectiveness in meeting the problems outlined than carefully elaborated statutes. In final analysis, even hospital facilities remain a professional responsibility. Nevertheless, we realize, if for practicality's sake alone, that definite ways must be mapped out.

The direction and nature of the rules and regulations adopted in Michigan can be shown by a few excerpts. The relation of these to the findings of the maternal death studies need not be spelled out.

1. "5.31 There shall be readily available the services of a clinical laboratory for complete blood counts, simple typing, cross-matching and urinalysis."

2. "5.41 in hospitals licensed for more than three maternity beds, equipment shall be available for diagnostic radiographic examinations."

3. "5.621 Facilities for immediate blood transfusions and intravenous therapy and for the administration of parenteral fluids shall be provided by the hospital at all times."

4. "5.622 The staff policies covering the use of Pituitrin and other oxytocics during labor shall be posted in all delivery units."

5. "5.623 The staff policies regarding the use and administration of analgesics and anesthetics shall be posted in all delivery units."

6. "4.1 There shall be adequate and competent medical, nursing and nonprofessional staff to provide efficient supervision of medical, nursing and other services."

7. "5.12 The hospital shall encourage written consultation among staff members on all complicated cases or those with questionable diagnoses."

8. "6.6 The hospital shall be responsible for keeping and preserving accurate and complete case records on all patients admitted."

It is recognized and agreed that regulations have value only if they are enforced. This is admitted by the Chicago Health Department in their extensive report on infant deaths. In any field, and perhaps more especially in medicine, when regulations are unrealistic, complex, or arbitrarily restrictive, they are violated openly and are practically nonenforceable. In Michigan both the health department representatives and the investigators of the maternal deaths emphasize that the provisions contained in the rules and regulations as a part of the licensing act are actually accepted standards of good medical care. By realistic, specific help given to hospital administrators and medical staffs, acceptance and compliance have developed from their own desires for improvement rather than from the necessity of following the statute.

Deficiencies have been discovered by the investigators and the health department staff. As a result, a substantial number of hospitals have been given only provisional approval for their maternity departments. By law, provisional approval can be extended only for a period of three years. The commissioner insists that the regulations will be enforced. He intends that they will be revised constantly so as to reflect current and accepted standards of medical care.

The dramatic decline in maternal mortality rates in recent years has been paralleled by an increase in maternal death studies. We are willing to admit that these studies may have been a factor in reducing deaths due to childbirth. Nevertheless, we believe that the reduction has resulted mainly from general advances in professional skill and practice, increased availability and use of hospital facilities, and better economic and social conditions.

During the last few years maternal death rates seem to have become static. Opinion has been expressed that these deaths represent an irreducible minimum. It has been argued that while some improvement in the rates may occur, it will not be of any significant order. Obstetricians have been complimented upon their achievement. They now are being urged to devote their attention to the

prevention of infant deaths. Such complacency, in our opinion, is unwarranted and dangerous. However minimal maternal deaths may appear, it must be remembered that these women are dead and permanently lost to their families. Each year those who die from complications occurring during pregnancy and childbirth would equal in number the population of a good-sized community. In three of our midwestern states, one-third to over three-fourths of these deaths have been judged to be preventable. No minimum for maternal deaths should be set. If there must be one, it should be a *minimum of preventability.* This minimum, we insist, should be zero.

This appraisal of maternal death studies is based upon our personal experience with them. We have been members of various committees concerned with maternal welfare. We have investigated many of these deaths personally. We have made formal and informal inspections of several of the hospitals where a disproportionately large number of these deaths occur. We have been members of reviewing boards for the critical evaluation of the factors involved in these fatalities. Moreover, we are practicing obstetrician-gynecologists.

Such experience has impressed upon us the constancy of the pattern of obstetrical inadequacy. We are convinced that the lessons which can be learned from maternal death studies have not reached certain segments of professional practice or that they have been either ignored or not fully appreciated. As in the spiritual realm where those who least need guidance attend church regularly, the conscientious practitioner is effectively guided by the sermons inherent in maternal death surveys. We are certain that these studies will have practical value only if the thinking and actual practice of the recurrent offenders can be affected.

We believe that maternal mortality rates have become static because the present efforts at reduction are insufficient and are not directed realistically at the environment in which the deaths occur. Maternal death studies have detailed the environment. Licensing and establishment of regulations seem to be effective. Medical records have improved. Better facilities and assistance for the physician have been supplied by hospital administrators. However, unless obstetrical practice in deficient areas can be similarly improved, maternal mortality surveys cannot justify the costs involved or the time given them by highly skilled specialists. It is our bound professional duty to prevent death wherever possible and to search constantly for means of improving medical care. We believe that more practical and effective application of the lessons learned from maternal death studies can be made. Specifically, such application could be made along the following lines:

1. Publication in professional journals of the results of these studies as statistical reports as well as by illustrative but anonymous case reports.

2. Discussion of the preventable factors in each death with the physician concerned. This could be accomplished by letter. We believe it would be more effective if it were done on a personal basis by a member of the state or local maternal welfare committee.

3. Discussion of maternal deaths at hospital staff and local medical meetings by a panel of specialists selected by the state committee. This would assure discussion of the deaths. It would permit disinterested analysis and comment. It would give opportunity to present important advances in our specialty to those who most need them.

4. Organization of district or county maternal welfare committees under the guidance of the state committee. This would give effectiveness to the type of discussion suggested above. Local problems would become evident. Solutions to these problems thus would be facilitated.

5. Voluntary establishment of accepted standards of obstetrical care by practitioners and administrators. Broadly conceived and carefully enforced legislation would give them specific support. Notification of the committee's appraisal of the maternal deaths that occur in their own hospital sent to the administrator and the chief of staff would detail the necessity for such standards.

6. Use of direct mailing under the guidance of the state medical society of brief, specific, practical instructive material regarding the recognition and management of obstetrical complications to *all,* and we should like to emphasize the *all,* members of the state society. Fearless comment of professional shortcomings could be disseminated by this means without the hazard of creating bad public relations or of disturbing the lay peace of mind.

7. Constant education regarding the value and importance of early and continuous medical care during pregnancy. This, we insist, can be done most effectively by the physician himself in his own office.

8. By the force of our own example, establishment in the minds of the general public of the essentials of proper and adequate obstetrical care. The public still pays for its medical care. It should be confidently assured that it now buys the best possible in present-day medicine.

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Discussion

DR. L. BURDETT WYLIE, Lakewood, Ohio.—The authors have presented an excellent affirmative answer to the question proposed in the title of the paper. Such studies, I am sure we all agree, are essential to any adequate program for the improvement of maternal mortality rates.

The detail of conducting the survey, as well as the use that may be made of the information gained, will vary in different localities, but the mere knowledge that such a survey is being made is of the greatest practical value.

I can recall that when such studies were instituted in Cleveland, over twenty years ago, there was an increased alertness on the part of all men doing obstetrics. Any tendency to radical intervention on the one hand, or hopeful procrastination on the other, was reviewed by the individual doctor in the light of the possible necessity of justifying his handling of the case in a subsequent discussion meeting.

I am sure that even those men who refused to participate in these meetings did better obstetrics because they were anxious not to have any of their cases come up for discussion today.

The method of obtaining data outlined in the paper is excellent. As pointed out, the death certificate is of value only in locating cases for investigation. Proper classification can be based only on a careful consideration of detailed clinical history. This can best be prepared, as has been suggested, by a disinterested investigator who is familiar with the purposes of the project and who can assemble and present all the essential facts without distortion or prejudice.

The study and classification of these cases by a subcommittee is important. If there are more than a very few cases for presentation, each case deserves individual and detailed consideration, but in an open meeting this is impractical. Either the case would receive inadequate consideration or the audience would be exhausted—probably both.

The presentation of illustrative cases from the various clinical groups with their general discussion preserves the clinical value of these meetings, while classification and grouping of cases will point out dangers to be particularly guarded against.

As has been stated, hemorrhage, toxemia, and infection are generally found to be the greatest offenders. However, there may be changes. In the Cleveland area in 1935 deaths from abortion ranked as No. 1, infection No. 2, toxemia No. 3, and hemorrhage No. 4; but in 1952 in Cleveland, pulmonary embolus, amniotic fluid, air, or thrombus was the No. 1 cause of death. Chronic hypertensive disease was second, and hemorrhage was third.

In Cleveland in 1952 we encountered no death from sepsis, and we had one death from toxemia. Abortion, which caused 25 per cent of the deaths a few years ago, appeared only twice, and these will be eliminated when we are able to locate the character who has used compressed air in the uterus with the resulting air embolism.

As for determination of preventability and responsibility, this again is of great practical value, in spite of the difficulty of doing so with finality.

It is easy to assume that a certain death was inevitable; but, was it? In Cleveland we are inclined to feel that we practice a superior brand of obstetrics—a feeling probably held by the obstetricians from every other area represented here with respect to their own locality.

However, a recent analysis of our maternal deaths indicated that while the patient was a good risk and cooperated well with her obstetrician in 75 per cent of the cases lost, the professional care was judged to be completely adequate in only 40 per cent of the cases—a ratio which certainly does not justify complacency.

The authors state that the attending physician still is held responsible for the professional care given, a responsibility which cannot be assumed properly or effectively by any public health official. Their suggestions as to regulation of hospital administration, and so forth, I think, are completely in order; but there is a corollary to this principle of the physician being responsible:

We should realize that if the profession fails to police its own ranks, and fails to take steps to correct its deficiencies, then we have no grounds for complaint if the social workers or the publicity-minded and politically ambitious public health officials take over.

DR. CHARLES H. McKENZIE, Minneapolis, Minn.—The reduction in maternal mortality, which changed so rapidly in the past 25 years, now seems to have reached a standstill statistically and, as Dr. Longyear points out, some seem to think we have reached the irreducible minimum. Obviously the irreducible minimum is zero deaths, but, just as obviously, as long as people are people, this is impossible. Nevertheless, the reduction in mortality is remarkable. It is only within recent years that less than 10,000 mothers die in our country annually as a result of childbirth. In Minnesota in 1941, the year of our first maternal mortality study, our rate was 2.0 maternal deaths per 1,000 living births. In 1950, the year of the next survey, the rate was 0.6, and in 1951 the rate was 0.3 per 1,000.

The committee for these studies has assessed the preventable deaths as follows:

In 1941—82 preventable of 112 maternal deaths
In 1950—22 preventable of 69 maternal deaths
In 1951— 9 preventable of 27 maternal deaths

The preclusion of these preventable deaths is our goal as obstetricians.

This remarkable reduction in maternal mortality has been achieved by many factors: better standards of living; better medical care; more hospitalization, with the availability of blood, antibiotics, and anesthesia; the education of the public, especially the pregnant woman and her husband, in the benefits of good maternal care; and the psychological and educational effects of maternal mortality studies.

The discussion of the case reports of maternal mortality studies by doctors in groups at postgraduate courses, in medical society meetings, in hospital staff conferences, etc., has helped to prevent deaths and will continue to do so.

All the factors listed have resulted in high standards of maternal care. Good customs accepted by all can lead to good regulations and laws acceptable to all. Dr. Longyear points out that in Michigan such regulations have been "broadly conceived" and are willingly obeyed. These regulations which he has outlined are excellent but they should not be considered are laws with a penalty for nonobservance, but rather as specific instructions, compliance with which will lead to better and safer maternal care.

The late Russell Moe said in the closing remarks of his presidental address, "On Lake Superior lighthouses are a part of our daily panorama. They light the way for the mariner. I believe that maternal mortality surveys are lighthouses for the obstetrician. They warn him of the reefs of dangerous practices." To continue the metaphor, Dr. Longyear has presented some practical rules which will serve as buoys in the channels leading to the harbors of safe maternal care.

DR. LUELLA E. NADELHOFFER, Evanston, Ill.—This is an excellent example of a committee on a state level using a good means of improving obstetrical care. This is not the case in all of the committees throughout the country, as any of you know who are serving on maternal mortality committees. The methods used and the results and further work by the committees are by no means uniform.

The American Committee on Maternal Welfare is conducting a survey of these twenty maternal welfare committees which Dr. Longyear mentioned, and a few of the facts I can give you in a preliminary report:

Nineteen of these twenty committees collect and review cases. Ten conduct open professional meetings, and those of you who have attended such meetings at Philadelphia or Baltimore or Chicago know how stimulating and interesting such meetings can be. Four have correspondence with the attending physicians, and six publish abstracts of the deaths. Three publish abstracts with analysis of cause and preventability, such as those published by Margaret Hague.

A small number sponsor postgraduate courses for general practitioners, obstetricians, nurses, and midwives, and at the local level two distribute educational material to the professions. One state sponsors public education through newspapers, radio, and television. That state was Indiana.

I would like to stress the last points Dr. Longyear made, namely, the educational, the patient, and the public. To this end the American Committee on Maternal Welfare in the past year has established the first women's auxiliary to the Committee. This auxiliary was formed for fund raising, and also to stimulate the interest of nonprofessional women in the work of committees such as these.

I know that women are very much interested in problems of maternal welfare. They like to know that such a committee exists, and of course the physician can interpret what the committee is doing to the nonprofessional women. They could assist in getting some of the services that are needed in the hospitals, such as blood banks. They should know the need for nursing services, and perhaps they could help with that. The need for trained anesthesiologists might be one place where nonprofessional women could help out.

They are especially interested in the things they read in the newspapers, of course, about the Rh factor, natural childbirth, and so on. I believe it is the duty of maternal welfare committees and physicians in the local communities to accept this as a part of their task in educating the nonprofessional women.

DR. T. A. LEONARD, Madison, Wis.—I would like to outline our recently inaugurated program in Wisconsin.

I think Dr. Longyear offers some very practical suggestions for problems which have been considered by our group.

We have tried to adopt the principle of complete anonymity in our investigative studies for the physician, for the patient, and for the hospital. We have a panel of thirty physicians. When a maternal death is reported to the State Board of Health, a physician is then chosen to interview in the community (remote from his own locality) so that there will be no personal problem involved. This interview is summarized and goes back to a study committee, with all identifications removed, so that when a study committee works on it they have absolutely no idea who the physician or the patient or the hospital was.

Those reports are then reviewed by the study committee. At a meeting of the committee, the preventability is discussed and a summary of criticisms and recommendations is made. Following this, a report is sent to the attending physician, also to the hospital, if hospital problems were involved.

Our study is as yet new. Our statistical data so far agree very well with the factors causative of death as reviewed by Dr. Longyear. However, our list is headed by hemorrhage caused by the trauma of delivery. Second come the cases of toxemia that have been improperly managed; and third, medical complications.

Again we agree with Dr. Longyear that the matter of blood replacement and the hospital management in the recognition and care of toxemias of pregnancy have been a big factor.

The only reason I appear before you today is because statistical data as we accumulate them have no value except for academic purposes. Our big problem to date has been this: What are we going to do with this information after it is accumulated? How are we going to utilize it and still have in mind the protection of those involved?

Dr. Longyear has made some excellent suggestions as to how this material can be utilized, even when it comes to the factor of legislative matters involving both hospital and the conduct of the management.

DR. SUTTON (Closing).—Drs. Longyear, Ott, and I appreciate very much the opportunity to present this plea—I call it a plea—to you. I have a long list of things that might be discussed further in exquisite detail, but I do not believe anything would be accomplished by so doing.

We are quite content if we have served the purpose of calling attention to the fact that statistical reports and surveys and analyses are not enough, and that each of us must go back to his respective state and consider constructive programs to accomplish what we probably would not be able to accomplish if we did not have constructive programs.

HYSTEROSALPINGOGRAPHY—A SAFE DIAGNOSTIC AND THERAPEUTIC GYNECOLOGICAL PROCEDURE*

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THE history of hysterography began in 1909 when Nemenrow injected the uterus with a radiopaque solution and obtained roentgenograms of the uterine cavity. In 1914, Rubin and Carey demonstrated the feasibility of determining tubal patency or occlusion using Collargol. Heuser, in 1921, was first to use Lipiodol. In 1933, Molengo and Conte used the aqueous radiopaque Skiodan. Since the inception of a method to visualize the uterine cavity and Fallopian tubes some five hundred papers have been published reporting from one to 2,500 cases. I am sure, therefore, that this report is neither new nor basically different. I wish, however, to reiterate some of the aims and principles of this method for it is my impression that among us, generally, hysterosalpingography is a somewhat neglected gynecologic procedure except as a last resort. I do not wish to compare oil instillation with the widely practiced Rubin's test, nor to advocate it of itself as a panacea for the treatment of infertility, but merely to demonstrate that it is a safe procedure, that it provides a medium for positive and definitive diagnosis, and that the results of the administration of a substance other than gas have shown a high degree of therapeutic effectiveness.

This report covers 260 separate instillations in 213 patients of parity from 0 to iv (Table I).

TABLE I. NUMBER OF INSTILLATIONS

No. patients		213
No. instillations		260
Gr. 0	171	
Gr. i	55	
Gr. ii	23	
Gr. iii	5	
Gr. iv	6	

Safety of the Procedure

When one speaks in terms of safety it is necessary to consider the possible complications of a procedure. The most insignificant complication, which leads to no pathologic state, is pain. In only one instance in this series was there sufficient pain to cause us to discontinue the injection. This occurred in a case of marked bilateral tubal stenosis where extraordinarily high pressure was exerted. The characteristic pattern during instillation is a sense of lower abdominal fullness as the oil fills and distends the uterine cavity, unilateral

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or bilateral twinges as it passes the uterotubal junction and isthmic portions of the Fallopian tubes, and occasionally a mild sensation of heat in the rectum if there is immediate spill of any great amount from the fimbriae. In general, the degree of discomfort is directly proportional to the rapidity of instillation. Slow administration requires less volume of the medium and the degree of intraperitoneal foreign-body reaction is therefore minimal (Table II).

TABLE II. AVERAGE DOSAGE (C.C.)

	FIRST PLATE	SECOND PLATE	THIRD PLATE
Nulliparas	3	6	8
Multiparas	4	7	9

Intravenous injections have occurred although not in my experience (Fig. 1). I am unable to understand how this might occur unless there has been improper application of the instruments or the mucosal surface of the cervix or uterus has been traumatized upon the insertion of the cannula. It is for this reason that I feel the procedure should be conducted by one who is familiar with the patient's genital system and any abnormalities thereof. It is especially necessary to be aware of retroversion, of which there were 36 cases in this series. The sequela of intravenous injection is the possibility of oil embolism, an exceedingly rare complication.

Fig. 1.—Intravenous injection.

The literature reveals that generalized peritonitis has been the most common cause of the few fatalities attributed to hysterosalpingography. Apparently this has been due to injection in the presence of subclinical inflammatory disease. This is not a fault of the method but an unfortunate choice of the case. To my knowledge there have been no deaths reported since the availability of the antibiotics. I have experienced two instances of localized peritonitis. One was in a case of salpingitis and perisalpingitis in a unilateral hydrosalpinx where 20 c.c. of oil was instilled to demonstrate the size of the lesion. Recovery was spontaneous after four days. The other was in an in-

dividual with a history of pelvic inflammatory disease in whom the instillation of 5 c.c. of oil revealed a unilateral hydrosalpinx (Fig. 2). Against more prudent judgment high pressure was used, even though it did not cause pain, in order to visualize the opposite tube completely. The sequence of events on this supposedly unaffected side were salpingitis, parametritis, and localized peritonitis. A 12 cm. tuboovarian abscess was removed two weeks later. Cultures revealed *B. coli*. It seems wise, therefore, to proceed cautiously with patients who have a history of pelvic inflammatory disease, no matter how remote.

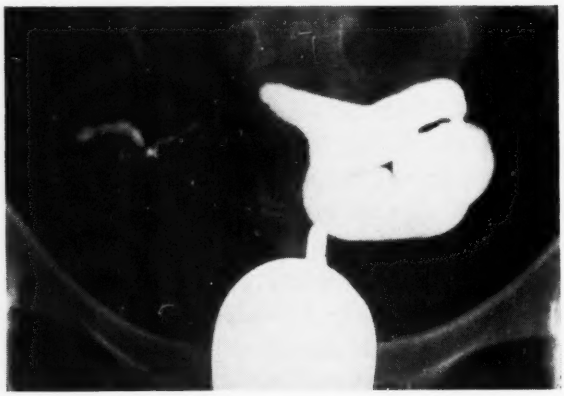

Fig. 2.—Unilateral hydrosalpinx.

The possibility of oil granulomas does exist although, with minimal volumes to limit the amount of the medium having access to the pelvic peritoneum, this complication should be entirely avoided. There does not seem to be any doubt that the presence of oil creates a foreign-body reaction within the pelvis in proportion to the amount of free oil passing into it. In one instance, not in this series, a large volume was instilled ten days before laparotomy. At that time oil granulomas were found involving the parietal and visceral peritoneum and omentum (Fig. 3). The tubal mucosa was perfectly normal. It is for this reason that I am content to demonstrate filling of the tubes only to the fimbriated ends and depend, rather, on a later plate to demonstrate spill and distribution.

TABLE III. DAY OF INJECTION

5th	8
6th	20
7th	26
8th	34
9th	17
10th	4
Over 10	3
Range: 5th-15th	

The criteria to be observed in contemplating salpingography are: (1) to be performed after the menses but before the day of ovulation; in other words,

only during the resting and early proliferative phases of the cycle (Table III); (2) never in the presence of a purulent cervicitis or vaginitis; (3) never during the presence of uterine bleeding, pregnancy, uterine or ectopic, or in acute or subacute pelvic inflammatory disease. The technical factors favoring safe execution of this procedure are: employment of slow instillation, using minimal volumes, after proper and atraumatic application of the instruments.

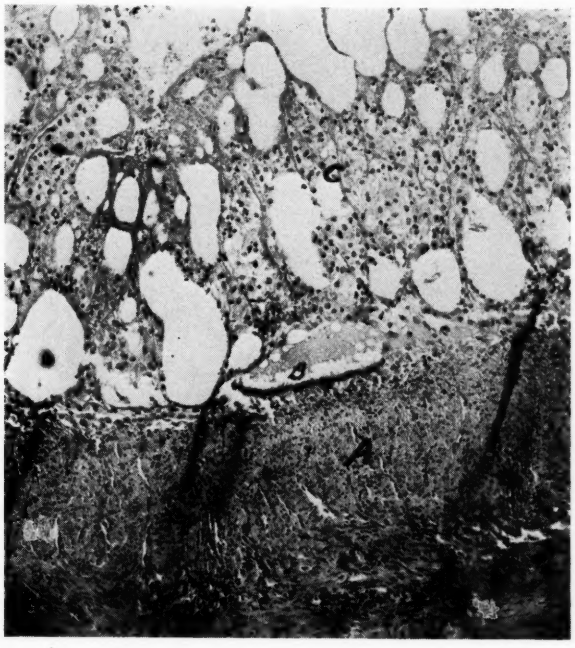

Fig. 3.—Oil granulomas. *A*, Myometrium. *B*, Portion of serosa. *C*, Exudate containing oil vacuoles, giant cells, and round-cell infiltration.

Diagnostic Value

Hysterosalpingography has reportedly been used as a means by itself in the diagnosis of endocervicitis, polyps, endometrial hyperplasia, adenomyosis, undiagnosed uterine bleeding, fibromyomas, tuberculosis, carcinoma of the endometrium, and tubal pregnancy. While I have no issue with the use of this procedure for these indications, and prefer other diagnostic methods, I believe hysterosalpingography was designed primarily for the diagnosis of tubal patency or occlusion and use it for this. During this investigation of tubal patency the roentgen diagnosis revealed the assorted normal and pathologic states which appear in Table IV.

In brief, I feel the extreme diagnostic value of hysterosalpingography is not only visual corroboration of the anatomically normal or occluded tubes but the concomitant presence of silent pathological states which in themselves might preclude conception or explain unsuccessful ones (Figs. 4-10).

Therapeutic Value

In evaluating the therapeutic effectiveness of a procedure or method it would be preferable to explain it in terms of observed physiologic response.

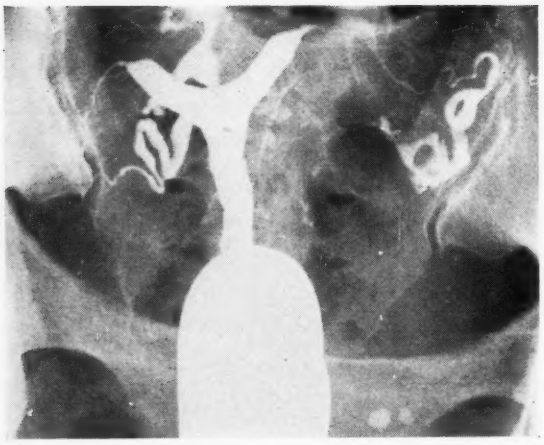

Fig. 4.—Uterus arcuatus. Frequently associated with late (five to six months) miscarriage.

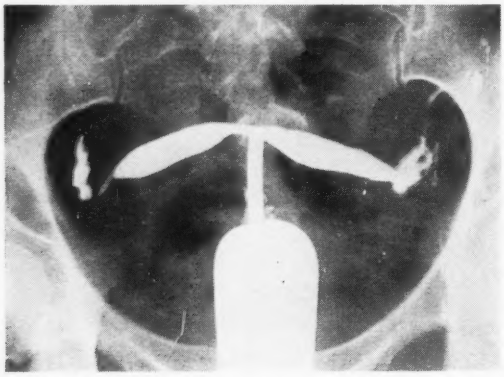

Fig. 5.—Uterus didelphys. Frequently associated with repeated early miscarriage.

Fig. 6.—Peritubal adhesions.

We must, however, conjecture in this respect at this time and interpret this method in terms of clinical response.

Infertility was considered present when no conception occurred after six menstrual cycles of connubial cohabitation. The duration of this state ranged from six months to twenty years (Table V). In the entire group con-

Fig. 7.—Tubal stenosis, a lesion frequently associated with tubal pregnancy.

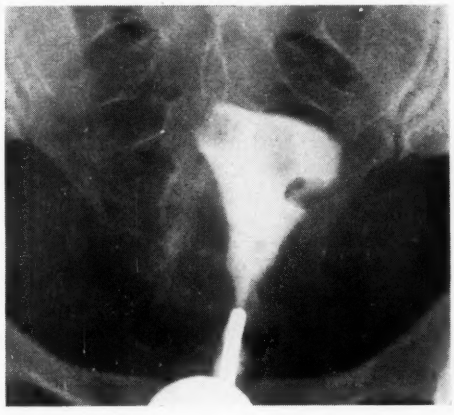

Fig. 8.—Nonsymptomatic submucous fibromyomas.

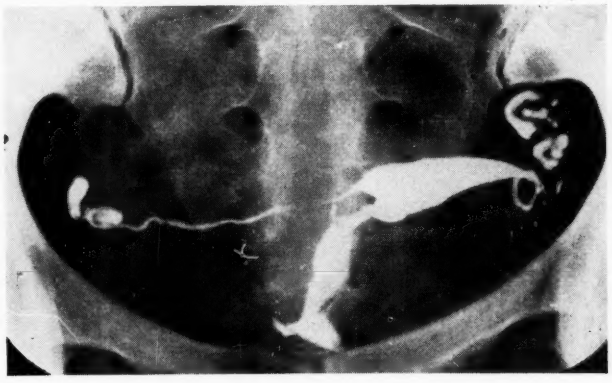

Fig. 9.—Right ovarian cyst. A 7 cm. mass occupied the right adnexa. Differentiated from a tuboovarian mass by salpingography.

ception was precluded due to the factors enumerated in Table VI. In 18 instances there were no absolute male or female factors which might contribute to infertility but in which conception did not initially occur. If we empirically define infertility as above, it seems reasonable to consider conception occurring within six cycles after salpingography directly related to the procedure. Of 166 pairs possessing no absolute factors precluding pregnancy (semen normal, one or more tubes patent), 109 conceived within this period (Table VII). In 37 patients gas insufflation had been negative. But more circumstantial in evidence that oil injection effected a physiologic response is the number of pregnancies, 32, that occurred in which the Rubin test had been positive one or more times at normal pressures (Table VIII).

What deductions may we properly make from these observations? In the instances in which the gas insufflation had been previously negative, we

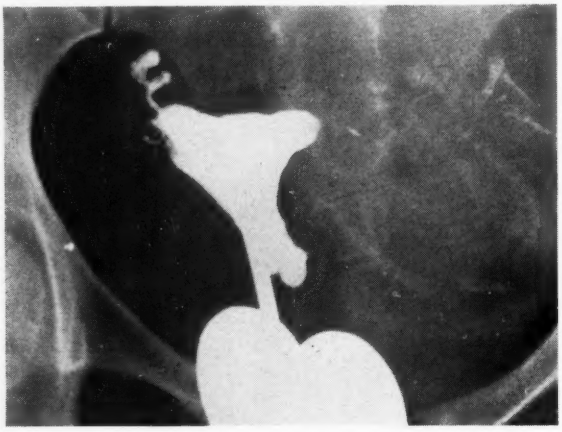

Fig. 10.—Large left tubal gestation. Salpingography neither necessary nor considered advisable.

TABLE IV. ROENTGENOLOGIC DIAGNOSIS

Normal	145
Unilateral occlusion	23
Bilateral occlusion	14
Unilateral hydrosalpinx	3
Bilateral hydrosalpinx	6
Peritubal adhesions	11
Tubal stenosis	10
Polyps	2
Submucous fibroids	2
Postoperative salpingoscopy	2
Ovarian cyst	1
Bicornuate uterus	7

TABLE V. MONTHS OF INFERTILITY

6-11	30
12-27	33
18-23	16
24	36
36	35
48	25
Over 60	40
Range: 6 months-20 years	

TABLE VI. NO CONCEPTION

Male factors	34
Female factors	25
Unknown	18
(Repeat salpingograms, 8 pregnancies)	
No follow-up	15

TABLE VII. CONCEPTION

No. of menstrual periods after salpingograms:		
0	24	
1	16	
2	27	
3	14	
4	7	
5	7	
6	14	109
Over 6	23	

TABLE VIII. CONCEPTIONS AFTER RUBIN TESTS

Conception after previous negative Rubin's tests	37
Conception after previous positive Rubin's tests	32
Negative Rubin's tests, positive salpingograms	49

might presume that the dense oil under constant pressure had established patency in previously obstructed tubes or tubes prone to spasm by overcoming the cohesive force of apposing surfaces of mucous membrane, or by expelling mucous plugs at the uterotubal junction. In the instance of repeated positive tests, however, another factor must be present. It appears logical to assume that this factor is related to the stimulation or enhancement of the inherent and physiologic contractility of the Fallopian tubes.

Conclusions

1. Hysterosalpingography is and can be a safe gynecologic procedure.

2. Hysterosalpingography offers a means of positive and definitive diagnosis of tubal patency or occlusion or uterotubal abnormalities which might be directly related to infertility.

3. These results indicate that hysterosalpingography effects more than mere establishment of an open passageway within the Fallopian tubes.

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Discussion

DR. A. J. WHITEHOUSE, Lexington, Ky.—Dr. Vogt's presentation was a great deal of reassurance to me. I have been doing hysterosalpingography for several years, and felt safe doing it. I do not feel that any procedure is entirely without danger, and I will not do a salpingogram on a woman until I have had a satisfactory report from the urologist on the fertility of the mate.

I do the salpingograms under the fluoroscope with the patient on the table, and I watch the progress of the oil. This gives me a great deal of satisfaction.

Only last week, when a patient whose general pelvic condition I was well aware of—which was perfectly normal to my manual examination—showed no passage of oil into the tubes, but suddenly showed a spread that we knew was a venous spread, we watched that oil with a great deal of apprehension, seeing it go into the inferior iliac veins, and we even watched it enter the chest.

As you know, there have been some excellent photographs of chest x-rays with generalized oil emboli in the lungs, without fatality. While that is a certain amount of reassurance, it is certainly something I do not care to have happen to my patient.

Doing this under the fluoroscope instead of as an office procedure, and then sending the patient to the radiologist for x-ray, gives me a greater feeling of safety.

I have had the same results that Dr. Vogt has had in finding negative gas insufflation reports and positive oil insufflation reports. It seems impossible that you could get oil where you cannot get gas, but that has been my experience, and I have been very well satisfied with the procedure.

DR. HERMAN I. KANTOR, Dallas, Texas.—One of the factors that Dr. Vogt pointed out was that there are certain dangers inherent in the use of oil. The dangers are minimal, but they are there. I should like again to point out, as I have done before in discussing this particular matter, in which I have been interested for a long period of time and which I have done many hundreds of times, that there is an absorbable medium which does give excellent results and which eliminates the possibility of oil emboli and oil complications. It seems to me that the minimizing of the possibility of intravenous injection should not be done. It does occur, and it occurs apparently with very little trauma in certain cases.

I also would like to stress one other point: The procedure, if used in a fairly large number of cases, sometimes shows evidences of unsuspected intrauterine pathology. Occasionally the hysterograms produce very satisfactory results, because we have discovered that even after dilatation and curettage polyps can easily be missed, and when diagnosed in this fashion they show up occasionally like sore thumbs in the beautiful hysterograms such as Dr. Vogt has shown.

DR. WILLIAM GERALD ROGERS, Oklahoma City, Okla.—I would like to emphasize the value of hysterograms performed under fluoroscopic control, and at the same time give a warning that there is a personal danger to the operator in doing this procedure.

Approximately one year ago I developed what was thought to be an allergic dermatitis on my hands. In attempting to determine the etiological agent, we rechecked our radiological equipment and reviewed our technique. With the simple use of a dental film with an opaque object, we were greatly surprised. The danger is permanent, so be careful!

DR. VOGT (Closing).—The statement that it is surprising that you can get oil where you cannot get gas does not apply to Houston or any other part of Texas, I guess. As far as iodism is concerned, that had been in the literature as one of the complications in years passed, but I think with our newer preparations this complication can be avoided.

ADRENAL VIRILISM IN THE FEMALE CHILD AND ADULT*

E. Stewart Taylor, M.D., and Robert H. Snow, M.D., Denver, Colo.

(From the Department of Obstetrics and Gynecology, University of Colorado School of Medicine)

THE reporting of a series of medical curiosities to a gathering such as this would not be justified on the basis of their rarity alone. A study of Nature's gross errors, however, will often give us clues which aid in the unraveling of her secrets. As the geologist gained insight into the material structure of the Earth's interior through a study of volcanoes, so has an investigation of the various types of virilism afforded a clearer understanding of the complexities of endocrinology that border on female infertility, certain types of amenorrhea, and hirsutism. The discovery of the usefulness of cortisone as a therapeutic agent for changing virilism to feminism in adrenal cortical hyperplasia is a step forward in this most interesting subject.[1, 2]

Adrenal virilism in the female may be congenital or acquired. The congenital type is secondary to adrenal cortical hyperfunction. The acquired forms of adrenal virilism may result from carcinoma, adenoma, or delayed hyperplasia of the adrenal cortex; or from certain rare ovarian tumors. This paper is a review of adrenal virilism in the female, and a presentation of illustrative case material from our own clinic.

The relationship of hyperfunction of the adrenal cortex to virilization of the female, and its endocrinology and biochemistry, are excellently recorded by Wilkins,[1] Hoffman,[3] Grollman,[4] Williams,[5] Talbot,[6] and Jailer.[7] The analysis of androgen steroids in the urine has aided in the differential diagnosis of masculinizing syndromes.[8-11] Masculinization of the female from ovarian arrhenoblastoma does not produce increases in urinary 17-ketosteroids; while adrenal cortical masculinizing tumors, adrenal cortical hyperplasia, and some ovarian adrenal-rest tumors do produce high levels of urinary 17-ketosteroids.[1, 2, 7]

Congenital Adrenocortical Hyperplasia

Many female children and adults who have been classified as intersexual individuals are patients with androgenitalism caused by congenital adrenal cortical hyperplasia. At birth, the parents and the attending physician are confused by the large clitoris and the hypospadias-like penis. The gonads and scrotum are not visible. A urinary meatus is seen to function below the clitoro-penis organ, but no separate vaginal opening is seen. Body growth, both by actual weight and measurement, is more rapid than normal. X-ray pictures of bone structure reveal a skeletal age in advance of chronological age. The enlarged clitoris can be amputated and the hidden vagina can be

*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

surgically exposed. Exploratory laparotomy is frequently done in order to confirm the diagnosis of congenital androgenital syndrome in the female, although Wilkins[2] feels that laparotomy is not always necessary. He believes that an elevated urinary 17-ketosteroid excretion that can be depressed by cortisone therapy is proof of adrenal hyperplasia. A retroperitoneal injection of air is performed in order to demonstrate the adrenal glands. The gonads are biopsied at laparotomy and the adrenals are explored. The normal anatomical relationships of the internal genitals will be found, but the uterus, tubes, and ovaries will be smaller than normal. This is because of the suppressive influence of excess adrenal androgens. Surgical removal of one or parts of both adrenal glands has not been successful in reversing congenital hyperfunction of the adrenal cortex.[1, 2] Daily doses of cortisone have been successful in suppressing the excesses of 17-ketosteroids excreted in the urine,[12, 13] and masculinizing symptoms have been reversed in some of these patients.[2, 7, 14-26]

The following two case histories are representative of androgenitalism secondary to congenital adrenal cortical hyperplasia.

CASE 1.—CGH, No. 51807.

Clinical History: This was a 7-year-old white girl admitted to the hospital on Feb. 1, 1953 (Fig. 1). The parents brought the patient to the hospital to "find out if the child was male or female." The referring physician expressed concern over the confused anatomy of the external genitals as evident at birth. When the child was 1½ years old the mother noted increased growth of the already prominent clitoro-penis. Pubic hair appeared soon thereafter.

Physical Examination: The child appeared to be 2 to 3 years older than her actual age. There was no breast development or axillary hair. The pubic hair was found to be abundant and the clitoris measured 5 cm. in length. The urinary meatus opened from the perineum into a urogenital sinus between the rectum and the clitoris (Fig. 2). There was no external evidence of a vagina. Urological examination demonstrated a normal bladder, normal ureters, and kidneys. The patient had normal control of micturition. A small vagina and cervix could be seen within the urogenital sinus through the cystoscope in normal relationship to the bladder and rectum. Retroperitoneal injection of air for contrast and radiographic study revealed the left adrenal gland to be slightly larger than normal.

Laboratory Data: The results of the routine laboratory data were normal. Other laboratory work included a normal Robinson-Kepler-Power[27] diuresis test, normal electrolyte pattern, normal fasting blood sugar, and a total serum cholesterol of 66 mg. per cent. The 17-ketosteroid excretion in the urine was 21 mg. in 24 hours (normal for this age is 2 mg.). The 11-oxysteroids were 0.34 mg. per 24 hours (normal). The basal metabolic test was reported as a plus 5. The eosinophil count was 176 per cubic millimeter.

Clinical Course in Hospital: On Feb. 19, 1953, the patient was given 75 mg. of oral cortisone, daily, for the purpose of suppressing the increased androgen excretion from the adrenal cortex. The response was very satisfactory in that eight days later the 17-ketosteroid level was 4.4 mg. in 24 hours. The 24 hour excretion of 17-ketosteroids has been maintained at between 1 and 4 mg. by the use of cortisone treatment.

Operation: Surgical exploration of the adrenal glands and the internal genitals was performed on April 6, 1953. A small uterus and small tubes and ovaries were seen. The gonads were biopsied and the histological examination proved them to be ovaries. The adrenal glands were explored and no tumor was discovered. The clitoris was amputated; the vagina was not established surgically. It was decided that this could better be done at an age near puberty. The postoperative course was complicated by mental depression of a few days' duration that disappeared spontaneously.

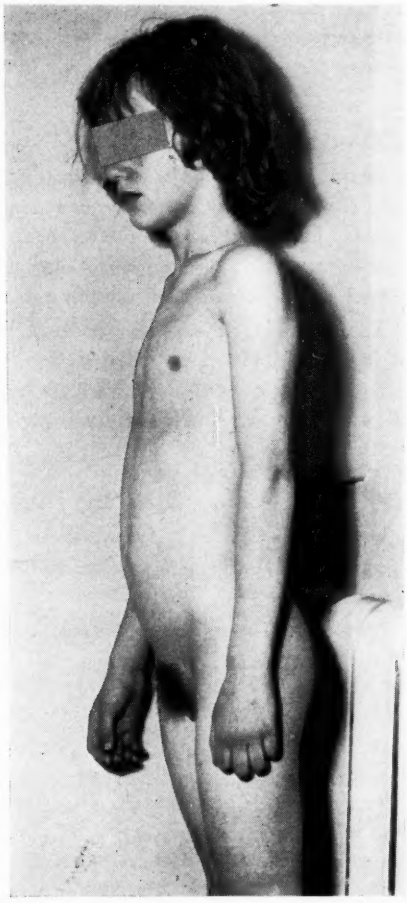

Fig. 1 (Case 1).—Child with heterosexual precocity, secondary to congenital adrenal cortical hyperplasia.

Fig. 2 (Case 1).—External genitals of child shown in Fig. 1.

Subsequent Course: The patient has received 75 mg. of oral cortisone daily. Her course has been entirely satisfactory and the 17-ketosteroids urine determination has remained normal. There has been no reduction in pubic hair at this time.

CASE 2.—CGH, No. 53592.

This was a 31-year-old white woman admitted to the hospital on May 4, 1953, with the principal complaint of masculinization. An enlarged clitoris was present at birth, and no vagina had been identified. Her voice had always been deep. Pubic and axillary hair were noted at age 5 years. Facial hair was present in the teens and required daily shaving at age 18. She had never menstruated. Body growth stopped at about the age of 15 years. The patient had always been regarded as a female and had considered herself one.

Physical Examination: The patient was muscular and short (Fig. 3). Her weight was 51 kilograms and she was 150 cm. in height. The facial hair was heavy, though well shaven. The breasts were masculine in appearance and no breast tissue could be palpated. There was a marked masculine pubic hair pattern reaching the umbilicus, and there was hair in the areolae of the breasts. A genital phallus was 4 cm. long (Fig. 4). The urethra opened into a urogenital sinus below the clitoris. Retroperitoneal air studies showed the adrenal glands to be slightly enlarged, particularly on the left. There was a hidden space cephalad from the urogenital sinus which appeared to be the vagina. A cystoscope was introduced into this, and a small cervix was visualized approximately 7 cm. higher in the canal. Retrograde pyelograms were normal.

Laboratory Data: The hemoglobin was 14.5 Gm. and the erythrocyte count was 4.9 million per cubic millimeter. White cells numbered 8,900 per cubic millimeter. The urinalysis was negative. The urinary 17-ketosteroids were 76.9 mg. in 24 hours, while the 11-oxysteroids were 0.4 mg. The basal metabolic rate was plus 30.

Operation: An exploratory laparotomy was performed on May 28, 1953. A small uterus was seen. The tubes and ovaries appeared normal though small. The gonads were biopsied and proved to be ovaries containing immature follicles. A small dermoid cyst was excised from one ovary. The adrenal glands were palpated and contained no tumor masses. The enlarged clitoris was amputated. A median incision of the urogenital sinus and perineal body exposed the hidden vagina (Fig. 5). A small amount of dilatation aided in the establishment of a practically normal, although small, vagina (Fig. 6). The patient was given supportive adrenocortical hormone therapy before and during the operation. This was continued for the first three postoperative days.[28] The postoperative course passed without event and the patient went home on June 5, 1953.

Two days after operation, cortisone treatment was begun for the purpose of depressing and controlling the virilizing symptoms. The treatment program is detailed below:

CORTISONE	URINARY 17-KS IN MG./24 HOURS
	5/ 6/53—76.9
5/30/53—50 mg. oral cortisone every 12 hours	6/ 3/53—58
	6/ 6/53— 8
6/17/53—25 mg. oral cortisone twice daily	6/17/53—10
7/ 2/53—25 mg. oral cortisone three times daily	6/24/53—25.9
	7/ 3/53—27.2
	7/ 6/53— 9.5
	7/30/53—12.2

On July 27, 1953, the patient had the first menstrual period of her life. She has menstruated regularly each month while receiving cortisone treatment. Each of these periods has lasted for three days. There has been no loss of energy or strength. The facial hair has become less profuse and of finer character. There has been noticeable breast development and the angular male face has become more feminine in contour (Fig. 7). The vagina, cervix, and uterus are essentially normal in size and shape.

Comments: These two patients illustrate the most common adrenal disorder of childhood. According to the older literature, each would have been classified as a female

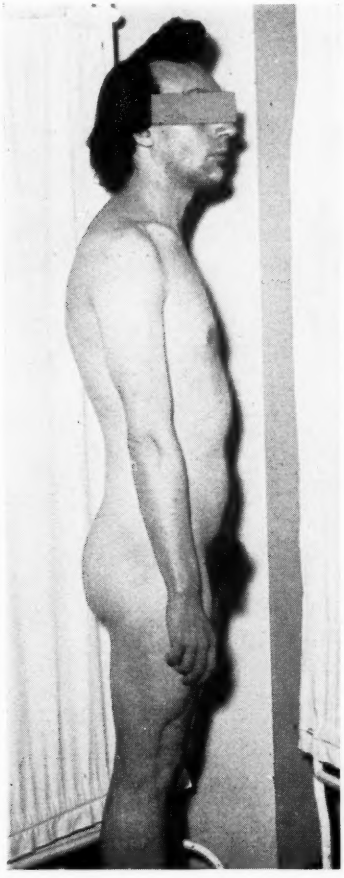

Fig. 3 (Case 2).—Adrenal virilism from congenital adrenal cortical hyperplasia (female pseudohermaphroditism), before treatment.

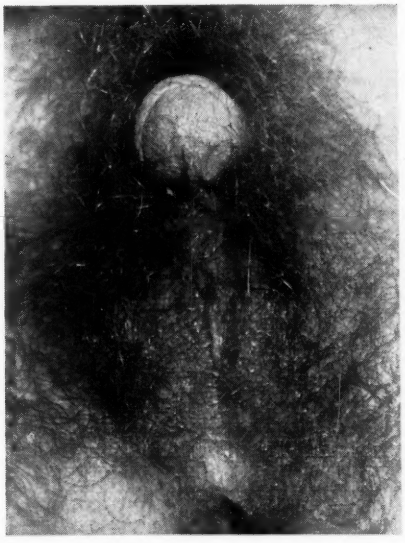

Fig. 4 (Case 2).—External genitals of patient in Fig. 3.

pseudohermaphrodite. The determination of the 17-ketosteroids and the 11-oxysteroids was most helpful in the differential diagnosis and proper classification of these patients. Both of them presented the history of a large clitoris at birth and anatomically confused external genital organs. The Müllerian organs were small as a result of the androgen domination. The urogenital sinus persisted as a single structure in each patient, and the clitoris resembled a hypospadic penis.

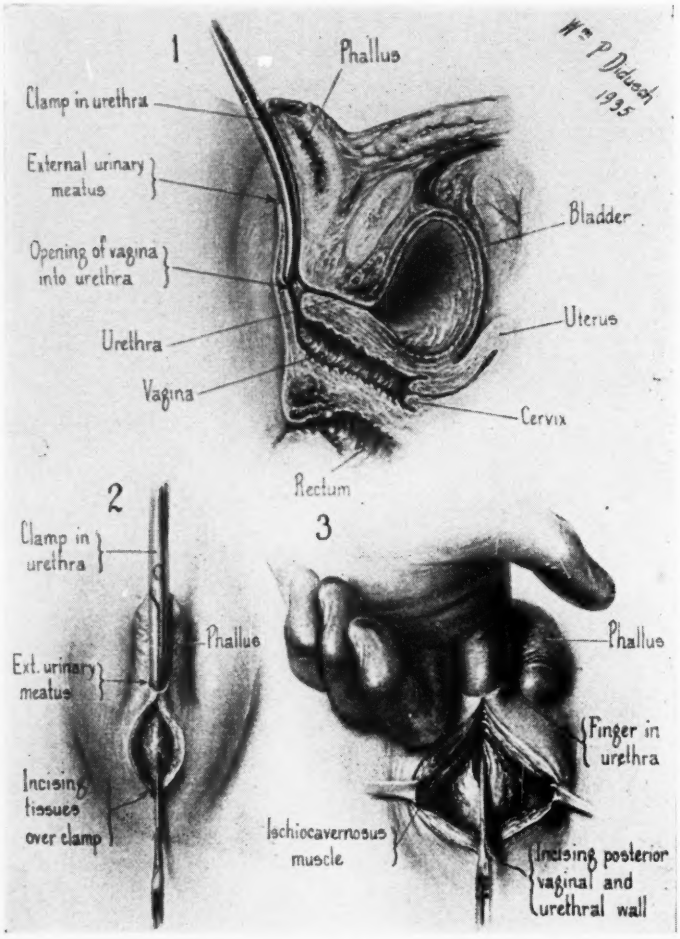

Fig. 5.—Anatomical relationships present in Cases 1 and 2, and demonstration of surgery necessary to establish a functional vagina. (From Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, 1937, Williams & Wilkins Company.)

The child demonstrated advanced bone growth. The adult patient was short of stature because of early epiphyseal fusion. She had the typical coarse body hair, high forehead, and the angular body features of the male. Breast development and menstruation had not occurred in the younger or the older patient, and such absence of development of breasts and menstrual function is expected in patients who have been subjected to virilizing influence.

Other conditions considered in the differential diagnosis were postnatal virilization, intersexuality, Cushing's syndrome, and virilization from ovarian or pituitary disease. An intersex patient may have external genitals identical with those of a patient with congenital adrenal hyperplasia. The 17-ketosteroids, however, are not elevated in an inter-

sexual individual, and the secondary sexual characteristics would be expected to develop at puberty. Virilization from adrenal pathology which develops postnatally is not accompanied by gross developmental abnormalities of embryonic origin. Masculinizing syndromes from arrhenoblastoma are not associated with increased 17-ketosteroids, and no patient as yet reported with arrhenoblastoma has been less than 15 years old.[29, 30]

Isosexual precocity of the pituitary, hypothalamic, or gonadal type as seen in small girls is not to be confused with heterosexual abnormal development illustrated by the patients with masculinizing signs.

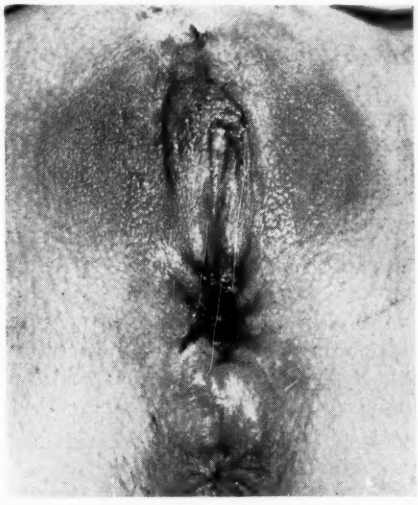

Fig. 6 (Case 2).—External genitals of patient shown in Figs. 3 and 4, after amputation of hypertrophied clitoris, and surgical establishment of vagina.

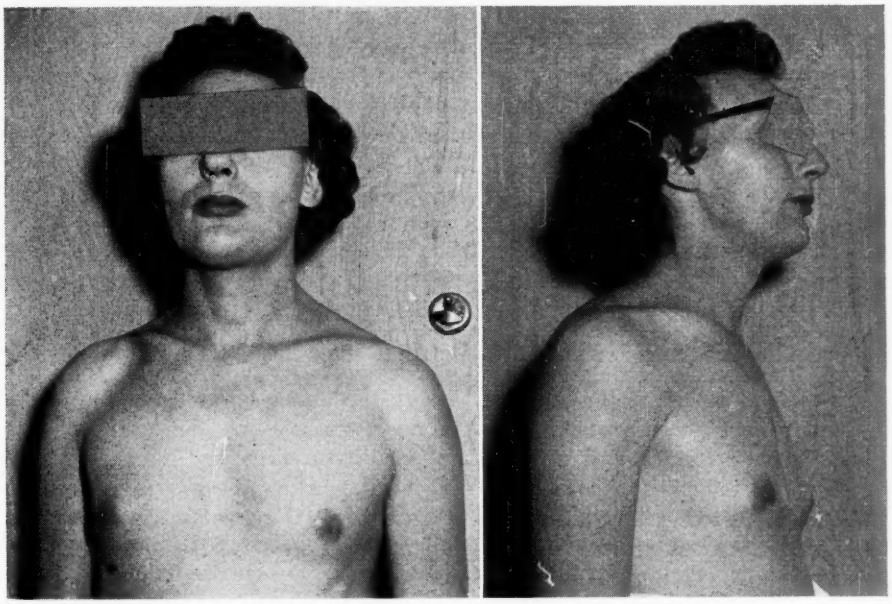

Fig. 7 (Case 2).—Reversal of virilism produced after four months of cortisone treatment.

Acquired Adrenocortical Hyperplasia

During childhood or early adulthood, virilism may be acquired as the result of adrenal cortical hyperplasia. Important in this connection is the fact of the subject having had normal genital anatomy at birth. The clitoris enlarges later, hirsutism develops according to a male distribution, and amenorrhea supervenes if menstruation had previously started. We have two such patients under treatment at the present time, and one of them is being reported today as illustrative of adrenal cortical hyperplasia, acquired type.

CASE 3.—CGH, No. 31735.

Clinical History: This was a 16-year-old girl who was admitted to the hospital on two occasions. Her first entrance was on Sept. 9, 1947, and the second was on Jan. 28, 1951. Her chief complaints were primary amenorrhea and hirsutism. At the second admission, at age 20, the patient had the additional complaint of decreased libido. The patient stated that she had never had a menstrual period and that hirsutism of face, arms, breasts, and legs, with male distribution of pubic hair, had begun at the age of 15.

Physical Examination: Physical examination revealed a blood pressure of 100/70. The patient was muscularly well developed and had marked hirsutism of the face, arms, and legs. Her body contours were of a masculine type. She had large hands and shoulders and small hips. There were no skin striae. The breasts were small, with a rather large amount of hair about each nipple in the areolar and periareolar areas. Pelvic examination revealed a small uterus and a hypertrophied clitoris. The clitoris was 3 cm. long and was 1.5 cm. in diameter. There were no adnexal masses palpated.

Laboratory Data: Admission hemogram was within normal limits. The urinalysis was normal. The basal metabolic rate was plus 21. Skull x-rays and intravenous pyelograms were negative. An aortogram revealed increased vascularity of the left adrenal area. The 17-ketosteroid determination was 38.8 mg. per 24 hours in 1947 and 26.8 mg. in 1951.

Operation: An exploratory laparotomy was done in 1947, as well as a diagnostic dilatation and curettage. The laparotomy revealed small ovaries, neither of which appeared functional, and infantile but otherwise normal internal genitals. The dilatation and curettage were not productive of any endometrial tissue. The patient was discharged in 1947 with the final diagnosis of primary amenorrhea and female pseudohermaphroditism. During the exploratory laparotomy, the adrenals were palpated and found to be normal in size and position. The patient was operated on again in January, 1951. This was for the purpose of determining whether an adrenal tumor had appeared in the interim between 1947 and 1951. No tumor was discovered.

Subsequent Course: The patient disappeared from our clinic until Oct. 6, 1953. Physical examination and medical history showed that her problem was unchanged. A 17-ketosteroid determination done on this date was 600 mg. per 24 hours. Cortisone treatment was initiated on Oct. 7, 1953. The dosage was 100 mg. of oral cortisone daily. On Oct. 22, 1953, after two weeks of cortisone therapy, her 17-ketosteroid level was less than 1 mg. per 24 hours. The dosage has been reduced to 75 mg. per day. Menstruation has not occurred.

Comments: The differential diagnosis consisted of ruling out a true intersexual condition, Cushing's syndrome, arrhenoblastoma, pituitary disease, and constitutional hirsutism. The urinary 17-ketosteroid level is elevated in adrenal hyperplasia, and the 11-oxysteroids are normal. The 11-oxysteroids are usually elevated in Cushing's syndrome.[31] The patient with acquired adrenal cortical hyperplasia will have no genital abnormalities other than the enlarged clitoris and infantile internal genital organs. Cortisone therapy has been used successfully in the treatment of these patients, in that menstruation has been established.[14, 20, 32-34] There are other reports[20-22] suggesting that the hirsutism has been reduced under cortisone therapy.

Adrenocortical Carcinoma

Acquired adrenogenital virilism may be caused by an adrenal cortical adenoma or by adrenal cortical carcinoma. We have had three such cases in our clinic, one in a female child, one in a young woman, and a third in a male child. The last is not being reported in this paper but is representative of the "infant Hercules" type. We have had no benign adrenal tumors that have produced virilism, but these have been reported by others.[35-39] Microscopic examination of an adrenal cortical tumor may be unreliable evidence of whether the tumor is benign or malignant. The ultimate decision as to the malignancy of the tumor may be settled only after observation of the patient's eventual clinical course.

From the time of birth until the tenth or twelfth year, virilization of the female is most frequently caused by an adrenal tumor.[29, 30] In the years after age 12, virilization is just as frequent from hyperplasia as tumor.[1] Virilization may occur as early as the second month of life and may advance rapidly. There is marked enlargement of the clitoris, accelerated bone growth, and the 17-ketosteroids are increased. The blood pressure may or may not be elevated. Pubic and axillary hair appear early.

Cases 4 and 5 are representative of acquired androgenital virilization secondary to carcinoma of the adrenal cortex.

CASE 4.—CGH, No. 14563.

Clinical History: This was a 19-month-old girl who entered the hospital on Sept. 13, 1949. The child was completely normal until 1 year of age, at which time the mother noted the growth of pubic hair and an enlarging clitoris. Acne appeared over the bridge of the nose.

Physical Examination: The blood pressure was 160/100. There was coarse pubic hair of the adult type; the vagina and labia were in their normal relationships, and there was a male distribution of hair over the body. The general appearance was that of a 2½-year-old infant. The clitoris measured 0.5 cm. in diameter and 1.5 cm. in length. The child seemed quite irritable. Psychometric tests were normal.

Laboratory Data: Routine laboratory tests were normal. 17-ketosteroids were 2.5 mg. per 24 hours (normal is 0.1 to 0.4 mg.). X-ray studies of the skeletal pattern showed a bone age of 3 to 4 years. X-ray examination of the abdomen and the perirenal areas was not helpful.

Clinical Course in Hospital: After observation and examination of the patient, it became apparent that the most probable diagnosis was an adrenal cortical tumor.

Operation: On Oct. 10, 1949, a solid tumor of the right adrenal cortex, measuring 3 by 4 cm. in diameter, was removed. This was classified as a carcinoma of the adrenal cortex.

Subsequent Course: Surgery was followed by 3,000 r of deep x-ray therapy directed over the right adrenal area. The patient was discharged from the hospital on Nov. 22, 1949, in good condition, and has been seen on the following dates in the outpatient clinic:

May 9, 1950: It was noted that the pubic hair was slightly reduced in amount. Generalized hirsutism and hypertrophy of the clitoris were still present.

July 10, 1950: The hair on the legs was less prominent, the clitoris was still enlarged.

Jan. 16, 1951: No essential changes noted. The patient was in good general health.

July 11, 1951: The clitoris was still hypertrophied. Hair persisted about the vulva but in considerably less amounts. Abdominal hair was reduced in amount. The growth pattern of the child was normal.

July 18, 1952: X-ray studies showed the patient to have a sketelal age of 5 years. Somatic growth was now less accelerated than previously.

Sept. 8, 1953: The patient is in kindergarten and is a normal child at this time. 17-ketosteroid examination revealed 0.5 mg. (normal) per 24 hours, and the 11-oxysteroids were normal. There was still a slight amount of pubic hair present. The generalized hirsutism has disappeared. The clitoris is the same size as in 1949, before treatment.

CASE 5.—DGH, No. 26059.

Clinical History: This was a 29-year-old gravida 0, admitted to the hospital on Sept. 7, 1949. Her entrance complaints were hirsutism of the face and abdomen since adolescence. The menarche was at age 14 and was followed by two menstrual periods. She had no more uterine bleeding until age 21. Menstrual periods then became regular, occurring every 28 days, lasting 4 days, and were normal until age 26. For the 3 years previous to admission to the hospital, she had experienced amenorrhea. During 5 years of married life, no pregnancies had occurred. The hirsutism had become progressively more marked in the past few years.

Physical Examination: The patient exhibited a male type of hair distribution and there was a palpable tender abdominal mass present in the left upper quadrant. The uterus was atrophied. The clitoris measured 3 cm. in length and 0.5 cm. in diameter. The breasts were normally developed.

Laboratory Data: Routine laboratory data were within normal limits. X-ray of the abdomen showed an abdominal mass in the region of the left kidney.

Clinical Course in Hospital: The diagnosis of virilizing adrenal tumor was made and the patient was prepared for operation with adrenal cortical extract, DOCA, and cortisone.

Operation: On Sept. 15, 1949, a left adrenal cortical tumor was removed. This proved to be adrenal cortical carcinoma. There was no evidence of metastases. The postoperative course was uneventful. The patient was kept on adrenal cortical extracts and DOCA until the ninth postoperative day.

Subsequent Course: The patient was discharged from the hospital on the seventeenth postoperative day and was in apparent good health except for her persistent virilism. She had re-establishment of the menses in January, 1950. She became pregnant and delivered a normal full-term infant on March 17, 1951 (eighteen months following surgery). Two additional pregnancies culminated in early spontaneous abortions. The patient was re-admitted to the hospital on July 15, 1953, because of generalized metastasis from the adrenal cortical carcinoma. The urinary 17-ketosteroid level was 2,400 mg. in 24 hours. The size of the clitoris and the hirsute characteristics had remained unchanged through the years from 1949 to date.

Comments: The differential diagnosis of virilism produced by an adrenal tumor should include a consideration of Cushing's disease, arrhenoblastoma, and adrenal cortical hyperplasia. The 17-ketosteroids are elevated in the presence of a functioning adrenal cortical tumor.[40] A suprarenal tumor can usually be demonstrated by air contrast x-ray studies. The genital organs are normal except for the enlarged clitoris and the undersized Müllerian duct organs. Exploratory laparotomy may be necessary in order to differentiate hyperplasia from tumor of the adrenal cortex. Virilizing tumors of the adrenal cortex will continue to secrete excess 17-ketosteroids under cortisone treatment. Heterosexual virilization apparently does not occur from pituitary or cerebral causes.[7]

Treatment consists of surgical excision of the adrenal tumor. This is done only after proper preoperative substitution therapy with adrenal cortical substance, cortisone, and ACTH. Removal of a functioning adrenal tumor otherwise may precipitate acute cortical adrenal insufficiency and death because of unilateral atrophy of the remaining gland.[41]

Ovarian Virilism

As gynecologists, our preoccupation with the pelvic organs constantly calls our attention to possible ovarian pathology for the origin of virilizing signs. The subject of adrenal-like tumors of the ovary which are capable of duplicating the symptoms and signs of an adrenal cortical functioning tumor arising in the suprarenal area is at present confused. If one classifies virilizing tumors of the ovary according to their metabolic effect and activity instead of their histological characteristics, the confusion is considerably less. The literature mentions hypernephromas, adrenal rest tumors, musculin-ovoblastomas, and masculinizing luteomas of the ovary that may produce virilization. A study of the case reports impresses one that the gynecologist and the pathologist have been describing these tumors as the blind men described the elephant. Schiller,[42] Barzilai,[43] Dockerty,[44] Curtis,[45] Novak,[46] and Herbut[47] believe that the virilizing lipoid-cell tumors of the ovary are essentially all the same tumor irrespective of name. Perhaps the tumors arising as they do from a multipotential organ like the adrenal cortex can be expected to exist in a variety of cell patterns. Ovarian adrenal-like tumors are functionally similar to adrenal cortical tumors and tend to produce virilization of the host, or Cushing's syndrome, dependent on which functional cells are most involved. There are admixtures of the classical adrenal virilization syndrome and the classical Cushing's syndrome. Curtis,[45] Kepler,[48] Greene,[49] and Rhoads[50] have reported adrenal-like ovarian tumors that have produced virilization. Kepler's report includes a review of the literature which adds another 13 cases of functional adrenal-like tumor of the ovary. His report displays the diversity of cell types, but tends to confirm that these tumors basically originate from misplaced adrenal cortical tissue residing in the ovary. Blewett[51] mentions 28 cases of virilizing lipoid-cell ovarian tumors reported in the literature to 1951.

To summarize the present information on masculinizing tumors of the ovary, the evidence seems to indicate that arrhenoblastomas represent one group, and that adrenal rest tumors form the other. The arrhenoblastomas produce a virilization of the host but do not change the 17-ketosteroid or 11-oxysteroid urinary levels. Adrenal-like tumors may produce virilism with a rise in the 17-ketosteroid excretion, or may produce Cushing's syndrome, while some may present a mixture of adrenal virilism and Cushing's syndrome.

Comment

The first step in the proper classification and diagnosis of sexual abnormalities is to establish, if possible, whether the syndrome is precocious development along the lines of isosexual or heterosexual female development. Precocious puberty in a young girl from constitutional, neurological, or ovarian causes is isosexual development and is to be distinguished from heterosexual development as illustrated by adrenal virilism of the female. Adrenal hyperplasia, congenital or acquired, superimposes masculine characteristics on the

female. Such a process may occur very early in life, in which case it is precocious. Or it may occur late in life and the most prominent characteristic is a reversal of feminine anatomy and physiology.

The clinical examination is very helpful in the establishment of isosexual versus heterosexual abnormalities in growth. Isosexual precocious puberty in the female is accompanied by early and rapid development of those organs normally dependent on estrogen for growth and sustenance. The breasts, uterus, cervix, and labia minora are large for the child's age. Menstruation occurs at an abnormally early age. To contrast the heterosexual precocious child's development, one has only to mention the sexual structures that hypertrophy under androgen stimulation. These are the clitoris and the labia majora. These organs are overdeveloped in the individual with heterosexual precocity. The male distribution of hair is characteristic of the heterosexual. Isosexual and heterosexual types may each have precocious pubic hair development. Precocious menstruation does not occur in adrenal virilism. Rapid bone growth is characteristic of precocious isosexual as well as abnormally early heterosexual development.

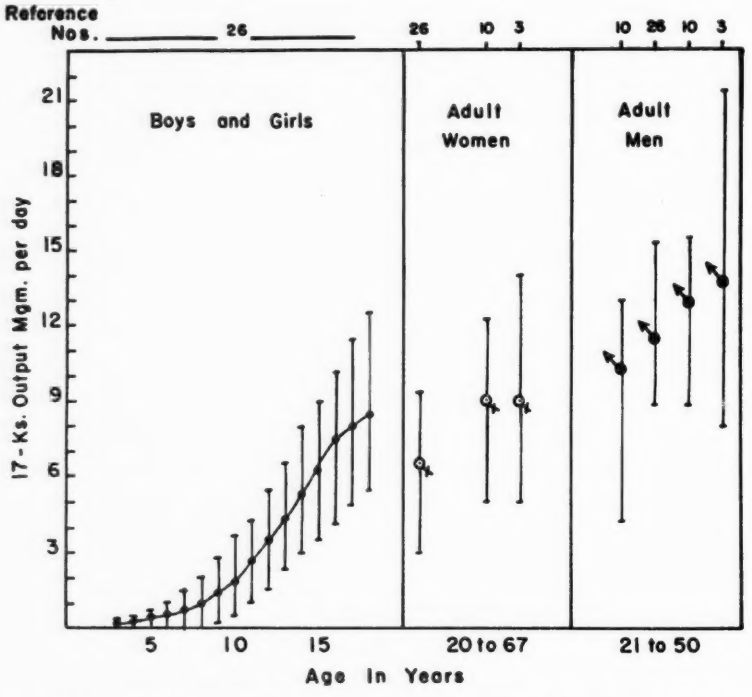

Fig. 8.—Urinary 17-ketosteroid values in milligrams per 24 hours according to age and sex. (From Talbot, N. B., and Butler, A. M.: J. Clin. Endocrinal. 2: 725, 1942, Fig. 1.)

The female pseudohermaphrodite patient may be successfully treated by a combination of surgery and medical treatment. Amputation of the clitoris and exposure of the recessed vagina are relatively simple. The virilizing effects from hyperplasia of the adrenal cortex can be arrested and reversed to some degree by using cortisone. The cortisone may depress ACTH activity

from the pituitary gland, or it may have a specific cytotropic effect on the androgen-producing cells of the adrenal cortex.[7] The hypodermic administration of cortisone is thought to be even more efficient than the oral administration. Wilkins[2] recommends 50 mg. of intramuscular cortisone, daily, at the onset of treatment. The depression of elevated 17-ketosteroids in the urine to normal levels is prompt and will be noted in the urinary assay in one week or sooner. The objective is to reduce and maintain the urinary 17-ketosteroid levels at physiologic amounts (Fig. 8). The maintenance dose of cortisone is 50 to 75 mg. each day taken by mouth. In infants and small children the dose will be less. While the cortisone is being administered, the blood pressure, urinary sugar, and general condition of the patient should be watched, so that undesirable changes in the metabolism of the patient that might lead to a syndrome similar to Cushing's do not occur. The information thus far suggests that cortisone therapy will have to be maintained for the life of the patient, and that adrenal atrophy has not occurred as the result of prolonged cortisone therapy.[2]

Summary

Five cases of adrenal virilism have been presented. Two are congenital adrenal hyperplasia, resulting in pseudohermaphroditism, one is acquired adrenal hyperplasia, and two are virilism from adrenal cortical tumors. The methods of diagnosis and treatment are presented, with special emphasis on the cortisone treatment of adrenal virilism secondary to adrenal cortical hyperplasia.

Conclusions

1. Adrenal cortical hyperplasia causing virilism in the female may be successfully treated with cortisone.

2. The anatomical abnormalities in the female produced in utero by adrenal cortical hyperplasia usually can be corrected by rather simple surgical procedures.

3. Urinary assays of 17-ketosteroids and 11-oxysteroids are essential in order to classify properly the causes of virilism in the female child or adult.

We wish to thank Drs. Harry H. Gordon and Robert H. Alway for the use of Cases 1 and 4, Dr. M. E. Peck for the use of Case 5, and Dr. Lyman Mason for Case 2.

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Discussion

DR. A. B. HUNT, Rochester, Minn.—Any presentation such as this, which explains the physiologic background of gynecologic disease, should be welcome. Some tragic mistakes have been made in the past which are no longer excusable when one reads the literature on female pseudohermaphroditism and listens to such a clear exposition of it as this. Furthermore, the authors are to be commended for sticking closely to well-defined adrenal states of virilism in the female rather than including such "fringe" conditions as the Stein-

Leventhal syndrome, constitutional hirsutism with ovarian dysfunction and infertility, which may or may not be shown in the future to be in part due to faulty adrenal function. Such studies are not unwelcome but the present group of adrenal virilism syndromes with the well-documented cases is sufficient for one presentation and is less confusing.

There is apparently a difference between adrenal corticoidal hyperfunction in the adrenogenital syndrome, on one hand, and adrenal tumors, whether benign or malignant, on the other, in that among the congenital or infantile cases with hyperplasia the end product of the hyperfunctioning adrenal cortex seems to be an excess of androgens wherein adrenal insufficiency may even be present due to a quantitative decrease in the salt- and water-retaining adrenal cortical hormones. Thus the paradox of adrenal cortical insufficiency has been observed in some patients although hyperplasia of the adrenal cortex is present. However, with adrenal cortical tumors and in some cases of Cushing's syndrome due to hyperplasia of the adrenal cortex in the adult, corticosteroids are present in excess and among these patients treatment with cortisone has met with little success. The best treatment for these individuals seems to be bilateral subtotal adrenalectomy. Because of this, one can agree with Dr. Taylor's statement that in most instances the adrenals should be explored to make sure there is no tumor, malignant or benign. Certainly, if there is a lack of response from cortisone in reducing 17-ketosteroids in the urine, the idea of exploration should be seriously entertained in adrenal hypercorticalism that is acquired postnatally. Surgery for adrenal cortical tumors and for the rare adrenal types of ovarian tumors is always preferable because of the possibility of malignancy. If a tumor is removed and metastasis does not occur later the patient usually is permanently cured and requires no substitution therapy.

While it is true that most patients with arrhenoblastoma do not have great elevation of 17-ketosteroids there are cases with fairly appreciable elevations of these hormones in the urine. Faber has unpublished data concerning one patient with arrhenoblastoma who had 23 mg. of 17-ketosteroids in the 24 hour urine on two preoperative assays. This level fell to 11 mg. of 17-ketosteroids shortly after operation. He also has studied another patient who, 13 years after the removal of the arrhenoblastoma, had 31 mg. of 17-ketosteroids in the 24 hour urine. This patient died of an intercurrent infection. An autopsy was not available but she was suspected of having a metastasis even at this late date. He quotes Von Szathmary, who as early as 1937 stated that if the 17-ketosteroids rose postoperatively after the removal of the arrhenoblastoma it was indicative of a recurrence or metastasis.

I would like to ask Dr. Taylor if he knows of evidence as to whether the resumption of menses after cortisone therapy in adrenal cortical hyperplasia is ovulatory and if any known pregnancies have occurred among these young women.

The importance of adrenal, ovarian, and pituitary tumors causing amenorrhea has been emphasized by Randall, who found that 6 per cent of young women who complained of amenorrhea unassociated with pregnancy had functioning tumors in these glands.

I think Dr. Taylor would add two other reasons for treating these young women with cortisone. One is to regulate body growth. At first there is a tremendous growth, and then the closure of the epiphysis, and these patients are left somewhat stunted. That can be regulated better with carcinotherapy, reducing the 17-ketosteroids.

Also, of course, there is the psychological or even psychiatric side of it, which is most important, as Dr. Taylor has implied.

DR. JOHN DALE WEAVER, Austin, Texas.—I am interested in this paper because I was privileged to examine 1,014 people in our institutions, and I have seen many congenital deformities, so I have one word of warning:

I would call attention to the excellent diagram by Young, which Drs. Taylor and Snow have presented, showing that in these youngsters and infants when we see them, if they are examined under anesthesia and an opaque dye or some medium is placed in the

bladder, we find surprisingly often that cloacas can be developed by simply slipping a knife through a membrane that is not the vagina and is not an imperforate hymen. We have had two experiences that have saved us a catastrophe and helped the children for sixteen or eighteen years before anything could be done otherwise.

DR. R. R. MARGULIS, Detroit, Mich.—Our views are approximately the same as Dr. Taylor's. Our opinion is that hyperadrenalism varies. It is usually due to hyperplasia or malignancy.

I do not like to advocate medical investigation for the purpose of avoiding surgical exploration, which is a must, but it is interesting to postulate the possibility of making a correct diagnosis as to whether we are dealing with hyperplasia or a tumor prior to surgical exploration.

Dr. Zylagi and I, later confirmed by Dr. Wilkins, found that cortisone, through inhibiting the pituitary, is able to diminish the output of 17-ketosteroids. This is true only in hyperplasia, at least in our limited series of cases. When you are dealing with true neoplasm, this regulatory mechanism is apparently at fault, and it cannot be influenced as readily.

Therefore, before doing any exploration, we are giving those patients cortisone in amounts between 200 and 300 mg. for six days, and we follow the behavior of their 17-ketosteroids.

Again I would like to warn everybody who does this work not to take one value of the 17-ketosteroids as the only value, but to follow at least three or four and get the significant decrease. If you get a significant decrease, then you are more likely dealing with a hyperplasia.

I wonder what Dr. Taylor's experience has been in this respect.

DR. TAYLOR (Closing).—The discussants have brought out many things that add to our information. I am glad they were able to point them out.

The therapeutic test with cortisone to make a differential diagnosis between virilism from hyperplasia and virilism from a tumor is a good test, according to those who have had considerable experience with it. Wilkins, Talbot, and Jailer all are satisfied to use that as a therapeutic test, and fail to do an exploratory operation on the adrenals if they get a proper response to cortisone.

It is interesting that total adrenalectomy and subtotal adrenalectomy have not been of benefit in these patients so far. Hugh Young, in 1930 and 1932, did considerable surgery upon the adrenal glands for the purpose of reversing virilism to feminism, and his results were not good. He thought he was getting good results in his first reports, and then he died before he could follow the patients long enough, so Wilkins has taken up the follow-up of the patients. It now seems that the surgical attack was a failure. Perhaps different techniques will open something up in the surgical field.

One thing I thought was interesting was that in the last seven years I have seen approximately ten cases of virilism, and each time I always thought of the ovary first; but I still have not seen a case of virilization of the female from the ovary. It has all ended up around the adrenal gland. If that is other people's experience, it is fairly significant.

We have not studied ovulation on this one patient as yet, but we will. I know of no histories where conception or ovulation has actually been recorded.

MORBIDITY IN VAGINAL HYSTERECTOMY*

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DUE much to the reports by Heaney[1, 2] and others, the vaginal route is being utilized more and more for hysterectomy. Before the era of sterile technique it was chosen as a necessity over the abdominal route because of the lower mortality and morbidity rate. With the advent of sterile procedures and increased safety of abdominal operations, the vaginal route for removal of the uterus fell into disuse. Its present favor is due to re-evaluation by modern authors and realization that it is still a less disturbing procedure than abdominal hysterectomy and carries lower mortality and morbidity rates.

Since their advent synthetic detergents have been used for surgical scrubbings and in the medical field as cleansers. They have been shown by Lane and Blank[3] and by Speel[4] to be effective agents for removing fats, skin oils, and bacteria. It was felt advisable, therefore, to determine the ability of such an agent to reduce morbidity by its cleansing power.

Until use of penicillin vaginal suppositories was begun, most authors[5-10] reported morbidity in 20 to 40 per cent of cases following vaginal hysterectomies. In an effort to lower this rate, much has been done in recent years toward sterilization of the vaginal field before operation. Turner[5] found that the incidence of morbidity could be reduced markedly by the use of penicillin suppositories. He reported a decrease from 37.5 to 7 per cent. His work was criticized by Gardner, however, because of the choice of patients and because the operation was the work of more than one man. Cron and associates[6] were able to reduce the morbidity in their series from 42 to 23 per cent by use of penicillin suppositories. Their work also has been criticized on the basis that the operations were performed by 22 different surgeons. Turner, Moore[7] and others made bacteriologic studies following the use of penicillin suppositories and reported marked reduction in the bacterial count which tended to be correlated with the reduced morbidity and helped substantiate these results of lowered morbidity. It seemed advisable, therefore, to study the effect of penicillin suppositories on morbidity after vaginal hysterectomy in addition to the effect of detergent agents.

Method of Study and Procedures

One of us (Pratt) started the present study of morbidity after vaginal hysterectomy in 1949 and planned to continue it for at least four years. He planned to make a basic change in the vaginal preparation or in the antibiotic

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†The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

used routinely each year. The cases included were to be those of a single surgeon and all cases in which vaginal hysterectomy was performed by this surgeon during the period indicated were to be studied. This plan was carried out in general. Only one change was made in surgical technique during the four years and though the operating-room personnel varied as did the surgical assistants, there were no basic changes in instruments, suture material, or fluids given intravenously. In most cases the anesthetic was intravenous thiopental sodium (Pentothal Sodium) plus 50 per cent oxygen and 50 per cent nitrous oxide by mask. Curare was used only rarely, but intratracheal airways were used whenever any evidence of obstruction of the airway appeared.

The sole change in technique occurred in May of the fourth year of the study (1952). It had been customary to inject 1 c.c. of surgical Pituitrin submucosally on each side of the cervix, before the operation, in an effort to reduce oozing from the vaginal cuff. Twice in the fall of 1951 and twice in one morning in May, 1952, a severe drop in the patient's blood pressure occurred just as the initial incisions were being made. The patients were extremely pale, the blood pressure could not be obtained, yet the pulse rate was not correspondingly rapid and respiration continued. It was noteworthy that in all 4 cases the blood as seen in the vaginal incisions remained bright red and there was no evidence of anoxemia. Fluids and epinephrine were given intravenously, slight Trendelenburg position was utilized, and within 15 minutes in all cases the blood pressure was normal and the operation could proceed without difficulty. Nor did these patients have any postoperative difficulties. However, no Pituitrin was used since the fourth episode and in retrospect it is difficult to estimate any real increase in bleeding from the vaginal incisions.

A tight iodoform-gauze pack was left in the vagina in all cases for 48 hours and Foley catheters were left until the pack was out if there had been no repair of a cystocele. When a cystocele was repaired, the Foley catheter remained in the bladder for four days. Following removal of the indwelling catheter all patients were catheterized by the nursing staff twice a day or oftener until the residual urine was less than 60 c.c. on two consecutive occasions.

All patients became ambulant between 24 and 48 hours after operation and were encouraged to walk and move about, even when hampered by the indwelling catheter.

With the exception of sulfathiazole placed intraperitoneally at time of operation, no antibiotics were employed routinely in the cases included in the series during these four years. Nor were antibiotics supposed to be utilized at any time until notes had been made of the condition of the patient and of the reason for the use of the drugs. Procaine penicillin-G (Duracillin) was the antibiotic of choice for upper respiratory infection or thoracic complications, while sulfonamide preparations such as sulfisoxazole (Gantrisin) or Combisul, were most frequently used when there was dysuria, marked frequency, or

prolonged retention requiring many catheterizations. A positive urinary culture when the indwelling catheter was removed was not considered a reason per se for use of antibiotics.

The study was divided into four major compartments and one change was made each year.

1949.—The patients were prepared with a cleansing douche the night before operation and on the morning of the operation. In the operating room the vagina and labia were scrubbed for several minutes with soap and water, and the vagina was painted with Merthiolate. Before closure of the vaginal vault, 5 Gm. of sulfathiazole crystals was placed in the peritoneal cavity.

1950.—The patients received two cleansing douches the night before operation. Following each of these, 3 c.c. of sodium octylphenoxyethoxyethyl ether sulfonate (pHisoderm) was left in the vagina. The scrubbing in the operating room and the use of sulfathiazole remained the same as in 1949.

1951.—The patients received a single cleansing douche at night. The nurse then inserted into the vagina a suppository containing 100,000 units of penicillin. The scrubbing in the operating room and the use of sulfathiazole remained the same as in the two previous years.

1952.—The preoperative douche followed by a suppository containing 100,000 units of penicillin was used. The scrubbing in the operating room was continued but no sulfathiazole was used in the pelvis or in the vagina.

Criterion of Morbidity.—For purposes of this study morbidity was considered present in each case in which the temperature reached 100.4° F. (38° C.) or more on any two days following midnight of the day of operation. Though such a standard is not an excellent or even an accurate measure of true morbidity, still, it has been used frequently and it is at least an objective method of comparing the postoperative courses of similar groups of patients.

Cases Studied

All of the cases in which one of us (Pratt) performed vaginal hysterectomies during the four years, 1949 through 1952, were considered, a total of 593 cases. It was necessary to exclude 79 of these from this report. Seventy-eight were excluded because sulfathiazole was not given intraperitoneally or the penicillin suppository was not given preoperatively. In the other case a carcinoma in situ was considered present until the uterus was taken out vaginally. Then the pathologist found invasion of the endocervix and the operation was finished abdominally as a Wertheim hysterectomy. The patients excluded from the series showed a morbidity rate of 25.3 per cent, a figure that would have been considerably higher but only 2 of 19 excluded in 1949 had morbidity as defined herein (Table I).

TABLE I. THE MORBIDITY OF PATIENTS WITH VAGINAL HYSTERECTOMY, 1949-1952, INCLUSIVE

	CASES	MORBIDITY	
		NO.	PER CENT
Total cases	593	125	21.1
Cases excluded	79	20	25.3
Cases in series	514	105	20.4

The record of each patient was investigated with regard to morbidity, cause of morbidity, type of operation, length of stay in hospital, and the age of the patient. These data were grouped to demonstrate if possible whether the morbidity, the type of operation, the age group, and the length of the stay in hospital were correlated with the various methods of vaginal preparation and the intraperitoneal use of sulfathiazole.

The 514 patients in this series were rather evenly divided in the four years as shown in Table II. The numbers in the years varied only from 124 to 135. There was greater variation in the number of vaginal hysterectomies without repair. In 1950 only 21 patients did not have some form of vaginal repair whereas, in 1949, 38 patients had vaginal hysterectomy only. Again, 1950 is surprisingly low in patients in the 41 to 50 year group, but is highest in the other three age groups.

TABLE II. DISTRIBUTION OF PATIENTS WITH VAGINAL HYSTERECTOMY, 1949-1952, INCLUSIVE

YEAR	PATIENTS	VAGINAL HYSTERECTOMY WITH REPAIR	VAGINAL HYSTERECTOMY ALONE	AGE (YEARS)			
				40 OR LESS	41-50	51-60	61 OR MORE
1949	135	97	38	29	60	23	23
1950	124	103	21	31	28	33	32
1951	126	98	28	30	54	23	19
1952	129	102	27	27	46	27	29
Total	514	400	114	117	188	106	103

No attempt has been made to allow for or to exclude patients who had one or both tubes or ovaries removed, ovarian cysts excised, and the ovaries reconstructed or specimens removed from skin or breast for study. Nor have we in this study made any allowance for the preoperative condition of the patient. A number of the uteri were large and required hemisection or morcellation for removal. We felt that these would pretty well average out in the four years' work.

Results

Vaginal Preparation.—The effect of the vaginal preparation and the intraperitoneal use of sulfathiazole on morbidity is considered in Table III. All patients received cleansing douches the night before operation and in all the perineum and vagina were scrubbed with soap and water by the surgical team as soon as the patients were anesthetized.

Use of pHisoderm decreased the over-all morbidity 6 per cent, but preoperative use of the penicillin suppository in 1951 caused the most noticeable decrease in the occurrence of morbidity to 12.7 per cent. The next year when no sulfathiazole was used intraperitoneally, the incidence of morbidity rose to 17.8 per cent.

Vaginal Repair.—The effect of vaginal repair in addition to vaginal hysterectomy on the morbidity rate is shown in Table IV. With elevation of temperature as the definition of morbidity, we found little real difference in the occurrence of morbidity when we compared patients who had vaginal hysterectomy alone with those who had some form of repair in addition.

Surprisingly enough, the morbidity rate from vaginal hysterectomy alone was slightly higher (22.8 per cent) than that following vaginal hysterectomy and repair (19.8 per cent). This difference was accounted for entirely by the patients operated on in 1949. In the other 3 years there was a rather steady parallelism between the morbidity rates of the two groups of patients.

TABLE III. THE EFFECT OF THE VAGINAL PREPARATION ON THE MORBIDITY OF PATIENTS WITH VAGINAL HYSTERECTOMIES, 1949-1952, INCLUSIVE

YEAR	CONDITIONS OF STUDY	TOTAL PATIENTS	MORBIDITY	
			NO.	PER CENT
1949	5 Gm. sulfathiazole intraperitoneally	135	38	28.2
1950	pHisoderm night before operation 5 Gm. of sulfathiazole left intraperitoneally	124	28	22.6
1951	100,000 units of penicillin in vaginal suppository night before operation 5 Gm. of sulfathiazole left intraperitoneally	126	16	12.7
1952	100,000 units of penicillin in vaginal suppository night before operation No sulfathiazole left intraperitoneally	129	23	17.8

TABLE IV. THE RELATIONSHIP OF VAGINAL REPAIR TO THE MORBIDITY AFTER VAGINAL HYSTERECTOMY

YEAR	WITH VAGINAL REPAIR			WITHOUT VAGINAL REPAIR		
	CASES	MORBIDITY		CASES	MORBIDITY	
		NO.	PER CENT		NO.	PER CENT
1949	97	24	24.7	38	14	36.8
1950	103	24	23.3	21	4	19.0
1951	98	13	13.3	28	3	10.7
1952	102	18	17.6	27	5	18.5
Total	400	79	19.8	114	26	22.8

Stay in Hospital.—The average stay in the hospital of these patients is shown in Table V. Data relate to morbidity, to vaginal repair, and to the year. The figures were rather consistent and patients who had morbidity averaged about a day longer in the hospital than the other patients. When the vaginal walls were repaired in addition to the hysterectomy, the average stay of both groups was three days longer than for those who had hysterectomy alone. Vaginal preparation or the use of sulfathiazole did not appear to change in any way the duration of hospitalization.

TABLE V. POSTOPERATIVE DAYS IN THE HOSPITAL FOLLOWING VAGINAL HYSTERECTOMY STARTING WITH THE DAY OF OPERATION AS THE FIRST DAY

YEAR	DAYS IN HOSPITAL AFTER OPERATION			
	MORBIDITY		NO MORBIDITY	
	REPAIR	NO REPAIR	REPAIR	NO REPAIR
1949	12.4	7.7	9.5	6.8
1950	11.5	7.5	10.6	7.3
1951	12.5	8.3	11.0	7.6
1952	10.6	8.2	10.6	7.0
Average	11.7	7.8	10.4	7.2

Age.—In this study we found that age per se played a part in determining both the stay in the hospital and morbidity. The older patients averaged a somewhat longer stay in the hospital (Table VI) but fewer had morbidity (Table VII). However, again we found no evidence that vaginal preparation influenced the stay in the hospital.

TABLE VI. EFFECT OF AGE ON DAYS IN THE HOSPITAL FOLLOWING VAGINAL HYSTERECTOMY*

YEAR	DAYS IN HOSPITAL AFTER OPERATION FOR VARIOUS AGE GROUPS			
	40 OR LESS YEARS	41-50 YEARS	51-60 YEARS	61 OR MORE YEARS
1949	8.2	8.9	10.7	10.3
1950	8.9	10.2	10.7	10.9
1951	8 9	10.7	11.1	11.1
1952	8.8	9.8	11.1	10.2

*Day of operation is considered the first day.

TABLE VII. THE MORBIDITY AFTER VAGINAL HYSTERECTOMY WITH AND WITHOUT VAGINAL REPAIR IN RESPECT TO THE PATIENT'S AGE

AGE (YEARS)	WITH VAGINAL REPAIR			WITHOUT VAGINAL REPAIR		
	PATIENTS	MORBIDITY		PATIENTS	MORBIDITY	
		NO.	PER CENT		NO.	PER CENT
40 or less	64	15	23.4	53	16	30.2
41-50	145	29	20.0	43	8	18.6
51-60	98	22	22.4	8	1	12.5
61 or more	93	13	14.0	10	1	10.0
Total	400	79	19.8	114	26	22.8

Year of Operation and Age.—The number of patients who had vaginal hysterectomy but no repair was too small to give either consistent or significant figures when an attempt was made to break them down into the 4 years of this study. The 400 cases of vaginal hysterectomy with vaginal repair, however, were sufficient to warrant grouping them according to the year in which the operation was performed (Table VIII).

Again in this study there was little change in any age group when pHisoderm was used, but when 100,000 units of penicillin was used preoperatively and 5 Gm. of sulfathiazole was given intraperitoneally, as in 1951, morbidity was the lowest in all groups of patients but those 51 to 60 years old. Use of the 100,000 units of penicillin and no sulfathiazole as in 1952 gave the second best results for patients 41 to 50 years of age and the best results for those 51 to 60 years of age.

Causes of Morbidity

The causes of the morbidity as determined from the temperature charts are listed in Table IX. Fifty (47.6 per cent) of the 105 patients in the entire series who had morbidity had physiologic morbidity. By "physiologic" we mean no organic cause for the elevation of temperature which usually occurred on the second and third postoperative days and subsequently returned to normal. In a similar study in 1951 of morbidity after total abdominal hysterectomy, we[11] found that physiologic morbidity occurred in 64 per cent

of the cases in which there was morbidity. The criteria of morbidity were the same as in this paper. In the four years covered by this study of morbidity after hysterectomy, physiologic elevation of temperature occurred in 44 to 53 per cent of the cases in which morbidity occurred. This rather even distribution over the four years seems to indicate that although this method of determining real morbidity is far from satisfactory, at least it is reasonably consistent for the purpose of comparing series of patients.

Table IX shows the rather even distribution of what might be termed "true morbidity" regardless of temperature in this series of cases. We could exclude physiologic morbidity, and if we re-examined the clinical records we probably could add to the cases of true morbidity an occasional case because of unusual pain or discomfort or delayed ambulation or even rectal impaction. Both the cases of morbidity and those without morbidity are spread over the four years with the exception that the 5 cases of infection of the vaginal vault or cellulitis all occurred in the first two years of the study; however, it is obvious that in dealing with figures this small only 1 or 2 cases would change the picture completely.

Six patients had thrombophlebitis in the four years. Only 2 had thrombophlebitis of deep veins, 3 had thrombophlebitis of the superficial saphenous system, and 1 had only questionable thrombophlebitis. In addition, among the patients excluded from the study 1 had spontaneous thrombosis of the external jugular vein on the sixteenth postoperative day in 1950 and another had thrombosis of the deep veins in 1950.

The most serious complication we encountered in this series and one, of course, that contributed to the total morbidity was postoperative hemorrhage. When it occurred events moved rapidly. The longest interval between the hysterectomy and re-exploration was 10 hours, and in 3 cases it was 5 to 6 hours. By hemorrhage we do not mean vaginal bleeding controlled by a pack but a postoperative retroperitoneal hemorrhage requiring operation to control. Retroperitoneal hemorrhages occurred in 5 of these 593 cases and all 5 cases were among the 514 that were acceptable for this study. Only 3 of the 5 patients had enough temperature reaction to meet the criteria for morbidity and these 3 patients were dismissed from the hospital on postoperative days 9, 11, and 18, respectively. Bleeding came from vessels in the wall of the bladder in the last patient and at re-exploration it was necessary to place packs and drains around the bladder. A Foley catheter was left in the bladder for nine days after reoperation as the bladder was opened to determine whether bleeding was going on inside it. The patient had fever on the ninth, tenth, and eleventh postoperative days when the drains were removed, but otherwise had an uneventful convalescence. Four of the patients with hemorrhage had vaginal hysterectomy and repair and 2 of these 4 did not have any morbidity and were dismissed 9 and 11 days after operation. The fifth patient with hemorrhage who underwent vaginal hysterectomy without vaginal repair had morbidity after operation but was out of the hospital in 9 days.

TABLE VIII. THE EFFECT OF VARIOUS VAGINAL PREPARATIONS ON THE MORBIDITY OF VAGINAL HYSTERECTOMY WITH REPAIR WHEN STUDIED WITH RESPECT TO THE AGE OF THE PATIENT

	AGE (YEARS)											
	40 OR LESS			41-50			51-60			61 OR MORE		
		MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY	
YEAR	PATIENTS	NO.	PER CENT	PATIENTS	NO.	PER CENT	PATIENTS	NO.	PER CENT	PATIENTS	NO.	PER CENT
1949	15	4	26.6	41	12	29.3	20	5	25.0	21	3	14.3
1950	20	6	30.0	24	7	29.2	30	7	23.3	29	4	13.8
1951	16	1	6.3	43	5	11.6	22	5	22.7	17	2	11.8
1952	13	4	30.8	37	5	13.5	26	5	19.2	26	4	15.4

TABLE IX. CAUSES OF MORBIDITY IN VAGINAL HYSTERECTOMY

CAUSE	1949		1950		1951		1952	
	MORBIDITY	NO MORBIDITY	MORBIDITY	NO MORBIDITY	MORBIDITY	NO MORBIDITY	MORBIDITY	NO MORBIDITY
Physiologic	17	–	15	–	7	–	11	–
Hemorrhage and laparotomy	2	1	1	1	1	–	–	–
Postoperative vaginal bleeding	–	–	3	3	–	1	–	3
Hematoma	4	–	1	1	–	1	4	–
Urinary difficulties	7	4	5	9	4	13	6	8
Upper respiratory infection	–	–	1	2	3	–	1	2
Allergy	2	–	1	1	1	1	–	–
Abdominal distention	1	–	–	1	–	–	–	–
Pelvic cellulitis	1	–	–	–	–	–	–	–
Infections of the vaginal vault	3	–	1	–	–	–	–	–
Thrombophlebitis	1	2	–	–	–	1	–	2
Unknown	–	–	–	1*	–	–	1	–
Total	38	7	28	19	16	17	23	15

*Parotitis.

Little or no vaginal bleeding occurred and in none of the cases was there intraperitoneal bleeding of consequence. However, all 5 patients had suprapubic or lower quadrant masses and showed signs of loss of blood with some decrease in blood pressure and elevation of pulse rate. The condition of 3 patients was serious and in 1 infusion of blood was started in both arms before the patient was moved to the operating room. We made an attempt to control the bleeding of 3 of the patients vaginally but were unable to do so satisfactorily. We then immediately made a low abdominal incision for adequate exposure. The bleeding of all these 5 patients was controlled and all made rather rapid recoveries, only 1 being in the hospital appreciably longer than the general average for vaginal hysterectomy alone or with repair.

A sixth patient who had a vaginal hysterectomy without repair had bleeding from the left ovarian vessels that could not be controlled with certainty from below. The abdomen was opened immediately. She had a physiologic type of temperature morbidity on the second and third postoperative days and left the hospital on the tenth day.

Replacement of blood was a paramount consideration and each of these 6 patients received from 500 to 2,000 c.c. of blood during the emergency period. Alertness of the resident and nursing staffs in establishing the diagnosis early and thus allowing measures to be taken to control the loss of blood contributed greatly to the subsequent postoperative course.

Vaginal bleeding accounted for the morbidity in 3 other patients and was present also in 7 who had no elevation of temperature. This bleeding required sutures to control in 2, and vaginal packs in the others, but in none was the loss of blood such that transfusions were required.

Hematomas behind the vaginal vault or in the adnexa were diagnosed in 9 cases in which morbidity occurred and in only 2 other cases. Hematomas also may have been present in some of cases reported as physiologic morbidity. When hematomas were present, the patients usually had an elevated temperature that came down with drainage of the hematoma.

The urinary problems have not been emphasized since they were rather evenly distributed over the four years, and because, in the majority of cases in which retention or dysuria or both occurred, temperature was never high enough for morbidity to be considered. Retention was the primary urinary difficulty in the cases in which vaginal repair was associated. When morbidity occurred, considerable pyuria and dysuria as well as retention were associated and the condition was classified as cystitis. In the cases of retention in which morbidity did not occur there were relatively few complaints of dysuria and infection in the bladder seemed to be playing a minor role. There were no serious or prolonged urinary difficulties. Retention subsided in all cases with time and no fistulas developed. In 3 cases the bladder was opened in the course of the hysterectomy and retention catheters were left in the bladder for 9 days after operation. All 3 patients were out of the hospital in 12 or less days and in none was morbidity present.

Several of these patients who had physiologic morbidity had some degree of retention; however, the elevations of temperature were on the second and third days after operation, while the urinary difficulties did not begin until the retention catheter was removed on the fifth postoperative day.

Allen, in discussing the work of Turner,[5] questioned whether sensitization or allergy was noted after the use of penicillin vaginal suppositories. Six patients in our series had allergic reactions and 4 of them were morbid. One patient who was operated on in 1951 did not have elevated temperature but had an allergic reaction which we thought might have been a reaction to thiopental sodium. The allergic reactions of the other 5 in 1949, 1950, and 1951 probably were due to sulfonamides. One elevation of temperature occurred after the use of a sulfonamide (Combisul), a second patient had urticaria that could have been due to any of the medicaments, and a third patient had an elevated temperature from the second to the sixth postoperative day. While the final 2 patients had severe temperature reactions reaching 105° and 105.6° F., neither clinically seemed as ill as the temperature would indicate nor were the increases in the pulse rate commensurate with the rise in temperature. One was out of the hospital on the ninth and the other on the tenth day after operation. There were no instances of jaundice, hemolysis, or the like that could with reason be ascribed to antibiotics.

Summary and Conclusions

This study of a series of 514 cases in which vaginal hysterectomy with or without vaginal repair was performed by one surgeon indicated that the intravaginal use of a suppository containing 100,000 units of penicillin the night before vaginal hysterectomy is the most effective means of reducing

morbidity of any of the methods tried. The introduction of 5 Gm. of sulfathiazole into the peritoneal cavity helps but the increase in morbidity following the elimination of it as a routine procedure was not marked. In patients on whom hysterectomy and vaginal repair were done, the combined use of penicillin and sulfathiazole reduced the morbidity the most and this effect was primarily on the patients 50 years old or less. Sodium octylphenoxyethoxyethyl ether sulfonate (pHisoderm) is helpful in reducing morbidity but is not as effective as the vaginal suppositories of penicillin.

We ran no control series without any vaginal preparation or scrubbing as we were not trying to prove that the vagina and vulva needed special attention before operation on the vagina. We assumed that special attention was necessary, and we were endeavoring to determine which of several methods would give the best results.

The total number of cases in each year and the number of patients in each year who had vaginal repairs as well as vaginal hysterectomy were comparable. The age distribution in each year was relatively similar and the only major change in care involved the use of pHisoderm, penicillin suppository, or sulfathiazole intraperitoneally.

While we were encouraged by the low number of serious complications and almost complete lack of upper respiratory infections, still we were surprised at having to reoperate within a few hours on 5 patients because of retroperitoneal hemorrhage. There were also 10 with vaginal bleeding of mild to moderate degree and 11 others with hematomas of the vaginal vault or the deep pelvic spaces. Many of these complications we should be able to forestall by added attention to details and technique. Two cases of thrombophlebitis of the deep veins and 3 of the superficial veins and 1 of questionable thrombophlebitis in more than 500 cases give an incidence of about 1 per cent. No cases of allergy were encountered in 1952, and this is doubtless due to the discontinuance of the use of sulfathiazole as a routine part of the operation.

Urinary retention was numerically our biggest single problem and though it caused added days in the hospital few elevations of temperature could be blamed on retention alone.

The variation in vaginal preparation had no effect whatsoever on the stay in the hospital. Patients with vaginal repairs averaged three days longer in the hospital than those with no vaginal repair. When morbidity occurred patients were one day longer in the hospital than patients without any morbidity. We found also that the stay in the hospital averaged one to two days longer for older patients than for younger. However, morbidity was less frequent among the women past 60 years of age. These patients usually had vaginal hysterectomy and repair but the uteri usually were small and atrophic. Loss of blood was less in the older women, the operation went faster and the anesthetics were of shorter duration. All of these are factors in lowering morbidity.

From our study the following conclusions seem warranted:

1. The use of a temperature of 100.4° F. or more on any two days following the day of operation as a criterion of morbidity is an uncomplicated method of determining morbidity. It is not a satisfactory method of determining which patients are seriously ill or in trouble following operation. However, it makes the same errors consistently as is shown by the number of patients with physiologic morbidity in each year as well as the rather even distribution of patients who had postoperative difficulties without elevations of temperature. For these reasons it is a satisfactory method of comparing series of patients.

2. Use of a penicillin suppository before operation is an effective way of reducing postoperative morbidity.

3. The combined use of a 100,000 unit suppository of penicillin in the vagina the night before operation and of 5 Gm. of sulfathiazole in the peritoneal cavity is most effective of the methods in this series in reducing the morbidity after vaginal hysterectomy either with or without associated repairs of the vaginal walls.

4. As in all surgical procedures, accurate control of bleeding is of paramount importance. This is particularly true when operation through the vagina is performed in the depths of the pelvis. Hematomas and bleeding are major factors in postoperative morbidity and retroperitoneal bleeding requires early diagnosis and immediate treatment if complications are to be kept at a minimum.

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Discussion

DR. AARON E. KANTER, Chicago, Ill.—We at the Presbyterian Hospital of Chicago under the aegis of Dr. N. Sproat Heaney feel like missionaries in having helped bring on the resurgence of vaginal hysterectomy in this country. Because of this we welcome a report such as has been presented here with a review of so many personal cases of vaginal hysterectomy displaying so few postoperative problems. Such a study is of untold help to us in our proselyting for vaginal hysterectomy as against the abdominal operation for the treatment of many conditions. I have had a very personal interest in the use of the penicillin vaginal suppository preoperatively. I believe it was back in 1948 when Turner first began his pioneer studies on the reduction of postoperative morbidity by the use of the vaginal insert. He came to me after his first 25 case studies and spoke of the apparently amazing results. I was skeptical, yet I felt that if this method had such potential merit, it should be explored to the fullest extent. In order to help build up a

rapid log of cases, I permitted Dr. Turner to use my patients at Mount Sinai Hospital and I began this prophylactic treatment at the Presbyterian Hospital. The rest of the story is a matter of record in the medical literature.

Since the publication of that work, many of us have been using the technique routinely. We find that the morbidity has remained at about the same level as was originally stated. I feel that the work as reported by Turner and some figures I shall quote in a moment are a far better appraisal of technical procedural change than are those of Pratt because these represent the work of many surgeons of varying skills, including members of the house staff, whereas the results presented by the essayist are those from the hands of a very highly skilled surgeon. If the method proves successful in the hands of the more occasional surgeon it certainly will be efficacious in the practice of the expert. I believe that we should play up, rather than down, the fact that the preoperative use of the penicillin suppository will help all of us reduce our morbidity and we will thus encourage more surgeons to use the vaginal route for hysterectomy.

Dr. E. D. Allen has very kindly permitted me to use some figures he has compiled at the Presbyterian Hospital. In a series of 2,280 patients in whom the uterus was removed vaginally, disregarding the concurrent pathology and the concomitant addition of other surgery, the gross over-all morbidity was 13.2 per cent. This figure represents the work of all of us on the attending staff plus that of a succession of residents. It also includes patients who had vaginal plastic surgery, the removal of one or both adnexa, and even the removal of endometriosis, as well as some 30 cases in which there was postoperative hemorrhage. The figures to date at the Mount Sinai Hospital, under the same conditions, show a similar morbidity. The techniques vary somewhat between the two hospitals. No preoperative douching is done at either institution. The penicillin suppository is inserted the night before operation. At Mount Sinai Hospital, the vulva and urethral area are washed with soap and water before catheterization, and Tincture of Zephiran is painted on the vulva and in the vagina. At Presbyterian Hospital the vagina and vulva are washed thoroughly with green soap and water and painting with Tincture of Zephiran is then performed. Thus we see that with no douches and with a complete washing out of the vagina in one place and no washing in the other, the ultimate results as far as morbidity is concerned are the same.

An important factor in the reduction of postoperative morbidity has not been mentioned. That is the proper preoperative care and preparation of the patient. This is of especial importance in dealing with women in the older age brackets who, even though they seem to show no greater over-all morbidity, should be logically less able to combat infection than are their younger sisters. If all foci of infection are cleaned up, particularly dental sepsis and severe cervical and vaginal infections or ulcerations, the postoperative morbidity would be reduced. The effort used in getting these areas cleared of active infection can save days of hospitalization, discomfort, morbidity, and annoyance. All this is worth a short delay in operation date. Care also should be taken to see that the patient is in a proper state of nutrition, that her blood picture is an adequate one, and that her blood chemistry studies and electrocardiogram are within safe limits. Preoperative blood transfusion is a valuable procedure, and blood administered during surgery can forestall shock and the ravages of excessive blood loss.

DR. FREDERICK J. HOFMEISTER, Milwaukee, Wis.—The problem of morbidity in hysterectomy has been studied at Milwaukee Hospital. On one of the services (Hofmeister) 396 vaginal hysterectomies were performed from 1946 to the present date. Vaginal hysterectomy without plastic was performed in 33 instances. Morcellation was employed frequently when the size of the uterus presented a problem of delivery. Every hysterectomy, abdominal or vaginal, is preceded by exploratory dilatation and curettement. All major pedicles are secured by a figure-of-eight type of suture.

There were no deaths in the series.

There were no serious complications or critically ill patients except in one instance of repeated abdominal and vaginal hemorrhages necessitating 2 vaginal and 2 abdominal

attempts to control the persistent generalized oozing. The exact cause of the bleeding was never determined in spite of complete blood studies by Dr. A. Quick. The bleeding stopped suddenly and the patient promptly recovered. One additional patient was returned to surgery to control hemorrhage by laparotomy. Bleeding in this case could be traced to the ovarian artery. Not too much emphasis can be placed on the importance of directing as much care in securing the ovarian vessels as the uterine vessels. In only 3 instances were secondary vaginal procedures necessary to control postoperative vaginal bleeding.

We also gauge theoretical morbidity by the same standards as defined by the essayist. We are impressed by the lack of symptoms and the apparent well-being that accompanies this state of morbidity.

Of our entire series, 30.3 per cent of the patients were morbid by definition. The majority of these cases occurred before 1950. During this period (1946 to 1950) 107 patients came to surgery without special vaginal preparation and 50 of these were morbid. Potassium permanganate douches, Zephiran packs, and Mercurochrome packs were used in a small number of cases, too few to add significance to the data. Those recorded and analyzed seemed to show a higher morbidity than cases in which no preparation was used. In only 3 instances was a sulfonamide put into the abdominal cavity. The results are not significant to the study.

When penicillin suppositories were used in 147 patients, morbidity definitely decreased. Only 24 patients had evidence of morbidity, an incidence of 16.3 per cent.

Terramycin was employed in 126 cases and in 25.4 per cent of the patients morbidity was present.

By far our best results, as in the case of the essayists, were associated with the use of the penicillin suppositories.

It is evident to us from the study carried on thus far that the development of an accurate technique and accurate hemostasis contribute to a large extent to the reduction of the morbid state.

As indicated before, complications were few. Our greatest complication and problem is the persistence of a disturbing urinary residual. The function of the bladder still remains our big problem in many cases where cystocele and urethrocele are repaired.

In a lesser degree, serum collections in the region of the vault incisions, which spontaneously drain and correct themselves, are the other complications that add to the picture of morbidity.

DR. CHARLES J. SMITH.—Taking various items of their study out of context, one is impressed by the influence of combined antibiotics, age, and surgical complications in the production of morbid states. In analyzing the effect of the operation on these 514 women as a whole, however, one is constrained to compare the result with that of similar series without finding more than the standard of excellence we have been led to expect from the Rochester group. Certainly, their average morbidity rate of 20.4 per cent compares favorably with the best to be found in the current literature, but the importance of their contribution suffers by a lack of comparison with results obtained in previous years in the same institution.

Our own experience involves a series of 319 cases over a ten-year period in which there was an average morbidity rate of 24.76 per cent. This group of cases was subjected to no definite regimen of preoperative preparation and spanned a period of time which, in part, antedated the use of antibiotics. It was our impression, as the authors point out, that morbidity influenced but very little the need for prolonging hospital stay. It is a constantly recurring theme in most reports, as suggested originally by Jones, Edwards, and Beebe, that surgical morbidity rates cannot intelligently be compiled on the basis of obstetrical morbidity criteria and that some universally acceptable modification should be introduced into the literature. This contention is further strengthened by the authors'

finding that almost half of their cases of morbidity were without detectable organic basis, and that the serious complications such as postoperative hemorrhage were not reflected, either numerically or by degree, in the morbidity figures.

With these observations in mind, we have felt for some time that morbidity figures in surgical reports are of questionable value, since they neither demonstrate what is happening to the patient or change the outcome very much. As the authors point out, unfortunately it is the only yardstick we have, poor though it is.

I found it of considerable interest to see the lack in influence that vaginal repair had on the outcome, as well as the low rate seen in the women of advanced age. Pratt very properly points out that atrophy, operating time, and minimal bleeding may well have been factors, but the implication is that the vagina might be considered a physiological organ in itself and the advocated use of preoperative estrogenic modification of the vaginal epithelium is ill considered.

DR. RALPH E. CAMPBELL, Madison, Wis.—Sometimes the best symposia that one attends in conjunction with a meeting are held in hotel rooms. Early this morning I attended such a meeting, and the question at stake was, "What is the best way to control hemorrhage following vaginal hysterectomy, severe hemorrhage?"

We threw that question around and came to the conclusion that unless you have spot bleeding, so to speak, something that you can actually see, that you are sure you can pick up by suture or maybe by clamp, the best approach is to open the patient's abdomen.

I want to emphasize that. If you have severe bleeding following vaginal hysterectomy, the best approach is probably by the abdominal route. I noticed that Dr. Pratt emphasized that point, and I want to re-emphasize it.

DR. PRATT (Closing).—Twenty-two hundred cases with 13 per cent morbidity really is coming down to a minimum. Thirty cases of postoperative hemorrhage in that group, I think, is extremely satisfactory. It is very difficult to tell when you ought to call them postoperative hemorrhage and postoperative serum, and the like.

We had these 5 cases with real hemorrhage. In three cases I thought I might be able to find something in the vaginal vault to pick up the bleeding point from below, but in all three patients I had to go in from above, which we did right at the same session. In two we took out the tube and ovary that was bleeding. In another we picked up a bleeding point underneath the waist of the bladder.

Another one was a very miserable case, with bleeding in the wall of the bladder. Finally, working from above, we put in packs and drains beneath, behind, and on both sides of the bladder. We opened the bladder to see if there was bleeding on the inside. We found no bleeding point. We gave the patient five pints of blood, and she was out of the hospital in seventeen days without turning a hair, except that we had to leave the catheter in for five days.

I do not know what I could have done about three of those cases. One bled in the wall of the bladder, one in the ovarian pedicle, and one in the vaginal vault. Two of the hemorrhages were due to perfectly definite technical errors of commission in surgery. The first assistant had been with me quite a while, and I reached over to tighten the tie on the uterine pedicle. He knew I was going to tie it. He tightened the pull on it at the same time I did, and we gave it a pretty fair jerk. We sponged and we watched it for about fifteen minutes, and no bleeding occurred, so we went ahead with the surgery. In about five hours we opened the abdomen and retied the artery and the broad ligament.

In the fifth case the assistant knew the other assistant had one hand on the retractor and the other on the pedicle. I said, "Pull," and he pulled on the ovarian pedicle, and he took the ovary right out of the vagina. We watched, and there was no bleeding, but later we had to open the abdomen and take out the tube and ovary where the tie had slipped from one small artery.

ACUTE APPENDICITIS IN PREGNANCY, A TEN-YEAR SURVEY*

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THE diagnosis of appendicitis is frequently difficult in the very young, the very old, the obese, and the pregnant patient. We are concerned with the latter. Acute appendicitis is a serious abdominal condition and when it occurs during pregnancy it presents a problem of greater magnitude. The mother and fetus are exposed to dangers besides the usual complications and sequelae of pregnancy.

In 1947, a young primipara in the seventh month of pregnancy was admitted to the Obstetrical Service of The Grace Hospital and died shortly thereafter as the result of a ruptured appendix, without benefit of operation. We then reviewed all cases of appendicitis in pregnancy for a ten-year period, 1943-1952, inclusive. A preliminary study, 1943-1947, inclusive,[1, 2] has been reported in *The Grace Hospital Bulletin*, and *The Western Journal of Surgery, Obstetrics and Gynecology*. Since 1943, 126 appendectomies have been done on pregnant women. Of these, 45 cases were acute, with or without peritonitis, and 81 were reported by the pathologist as chronic, atrophic, obliterative, etc.

Roentgen Studies of the Appendix and Cecum During Pregnancy

In 1905, Fueth[3] investigated the displacement of the cecum during pregnancy. In 1932 Baer and associates[4] reported their observations on the displacement of the cecum and appendix in 28 pregnant patients. From a clinical standpoint, none of these patients had ever had appendicitis. Baer concluded, "During normal pregnancy there is a gradual shifting in the position of the base of the appendix from its normal low-lying position in the iliac fossa to one somewhat above the iliac crest near term. In addition, the long axis of the appendix changes from the normal downward and inward direction, first to the vertical, often curving around the uterine fundus. This gradual outward and upward displacement of the appendix by the growing uterus places the appendix well above the crest level, and therefore above McBurney's point. The colon also is pushed upward and curves around the uterine fundus, the cecum being crowded upward and outward, often being buckled on itself, because of the pressure exerted by the growing uterus." A return of the displaced viscera to their normal positions usually occurs within the first ten days post partum. These well-established findings, as will be shown later, may cause masking of the physical findings when the appendix is the site of infection after the fourth month of gestation. Fig. 1, taken from Baer, Reis, and Arens, shows the changes

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in position and direction of the appendix during pregnancy, and Figs. 2, 3, 4 show x-ray evidence of the displacement of the appendix and cecum at the end of the third, sixth, and eighth months, respectively.

Baer's[4] x-ray studies were made on patients who presented no subjective symptoms of appendicitis. In our series of 45 cases (43 operations), 41 per cent of the appendices were freely movable, while 59 per cent were retrocecal or fixed by adhesions (Table VI).

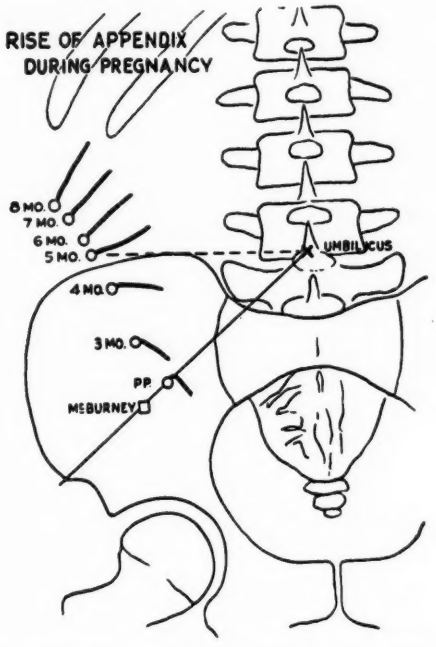

Fig. 1.—Changes in position and direction of appendix during pregnancy. (From Baer, Reis, and Arens.[4])

Incidence

Baer and his co-workers[4] report an incidence of 0.17 per cent in 16,543 pregnancies. Cosgrove[5] reports 0.072 per cent in 2,500 pregnancies. The fetal loss in Cosgrove's series was 16.6 per cent in 18 cases and there was one maternal death in the eighth month of pregnancy. Meiling[6] reports 21 cases of acute appendicitis in 49,681 deliveries with two maternal deaths; the fetal loss was 42.8 per cent. Mussey[7, 8, 9] reports an incidence of 2.0 per cent. Goodall[10] stated that he had seen 5 cases of acute appendicitis in 3,000 deliveries; while Greenhill[11] has had 3 cases in 2,500 deliveries. DeLee[6] is quoted to have said that in 30 years of obstetric practice, he had seen only 4 cases of appendicitis late in pregnancy. In our series of 44,242 deliveries at The Grace Hospital from 1943-1952, inclusive, there were 45 cases of pathologically proved acute appendicitis. This gives an incidence of 0.101 per cent. It is evident, therefore, that pregnancy does not predispose to appendicitis. In Mussey's[7, 8, 9] series of 75 cases he found that 50 per cent of the patients gave a history of previous attacks of appendicitis. Baer and associates[4] report a similar incidence in their

series of 28 cases of appendicitis in pregnancy. In the 45 cases of acute appendicitis comprising this study, 23, or 51.2 per cent, gave a history of previous attacks (Table II, *B*).

Stage of Gestation

It is the consensus that appendicitis is most frequently encountered during the first and second trimesters of pregnancy. In our series, the distribution is shown in Table I.

It is thought that the beginning displacement of the appendix and cecum plays more than a coincidental part in those cases with a history of previous infection. As shown in Table III, this was not true in our series. From our study, statistically at least, the displacement of the appendix after the third month of pregnancy is more significant than the history of previous attacks. Percentagewise, 64.5 per cent of the cases occurred after the third month of gestation irrespective of previous infection (Tables I, III).

TABLE I. PARITY AND DURATION OF PREGNANCY

	LOCALIZED TO THE APPENDIX (28 CASES)	WITH PERITONITIS (17 CASES)	TOTAL (45 CASES)
I. Parity.—			
A. Primiparous	12 (42.8%)	6 (35.2%)	18 (40%)
B. Multiparous	16 (57.2%)	11 (64.8%)	27 (60%)
II. Duration of Pregnancy.—			
A. First Trimester	12 (42.8%)	4 (23.5%)	16 (35.5%)
B. Second Trimester	11 (39.2%)	7 (41.2%)	18 (40.0%)
C. Third Trimester	5 (18.0%)	6 (35.3%)	11 (24.5%)

TABLE II. CLINICAL HISTORY

CLINICAL HISTORY	LOCALIZED TO THE APPENDIX (28 CASES)	WITH PERITONITIS (17 CASES)	TOTAL (45 CASES)
A. Immediate History.—			
1. Typical	21 (75.0%)	12 (70.5%)	33 (73.3%)
2. Atypical	7 (25.0%)	5 (29.5%)	12 (26.7%)
B. History of Previous Attacks.—			
1. No previous attacks	13 (46.5%)	9 (52.9%)	22 (48.8%)
2. Previous attacks	15 (53.5%)	8 (47.1%)	23 (51.2%)
C. Symptomatology.—			
1. Nausea	20 (71.4%)	12 (70.5%)	32 (71.1%)
2. Vomiting	17 (60.7%)	10 (58.8%)	27 (60.0%)
3. Generalized abdominal pain	22 (78.5%)	14 (82.3%)	36 (80.0%)
4. Right lower quadrant pain	18 (64.2%)	15 (88.2%)	33 (73.3%)
5. Two or more of above symptoms			33 (73.3%)
D. Duration of Symptoms (43 Cases Operated Upon).—			
1. 24 hours or less	20 (71.4%)	8 (53.3%)	28 (65.1%)
2. 25-71 hours	6 (21.4%)	5 (33.3%)	11 (25.5%)
3. More than 71 hours	2 (07.2%)	2 (13.4%)	4 (09.4%)

Symptomatology and Diagnosis

The symptoms of appendicitis are the same in the gravid as in the nongravid patient. As pregnancy advances, the pain is higher and more lateral.

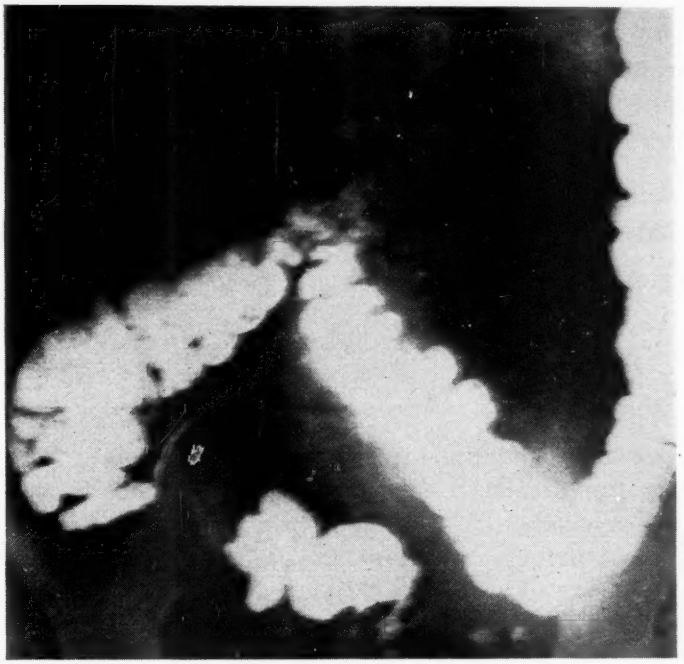

Fig. 2.—Appendix at end of third month of pregnancy. There is a little upward displacement of the cecum and the appendix points vertically. (From Baer, Reis, and Arens.[4])

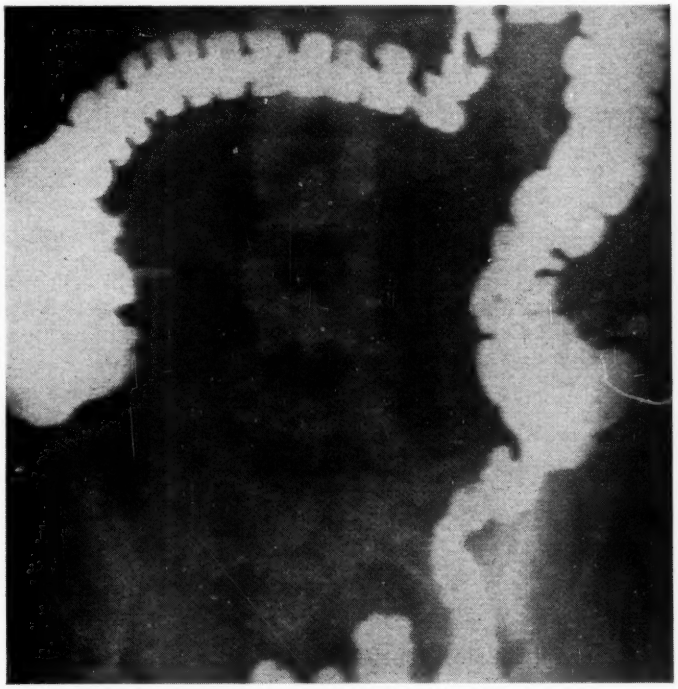

Fig. 3.—End of the sixth month. The appendix is horizontal and points medially. The cecum and appendix have been displaced upward and lie well above the iliac crest. (From Baer, Reis, and Arens[4])

Nausea, vomiting, muscle spasm, rigidity, fever, and leukocytosis are usually present in most cases, but the interpretation of these findings in the last six months of pregnancy may be difficult, because of the displacement of the appendix and cecum (Table II, *A*).

TABLE III. PREVIOUS ATTACKS

HISTORY OF PREVIOUS ATTACKS		FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER	AFTER THIRD MONTH AND IRRESPECTIVE OF PREVIOUS ATTACKS
No	22 (48.8%)	7	8	7	
			(68.1%)		64.5%
Yes	23 (51.9%)	8	11	4	
			(62.2%)		

The evaluation of symptoms referable to the gastrointestinal tract during pregnancy may prove rather confusing. This is especially true in cases of acute retrocecal appendicitis or in cases where the appendix is high in the region of the right kidney. We have had an experience with such a case, as has Meiling.[6] Neither of these patients had any prenatal care prior to being admitted to the hospital. Our case will be briefly outlined later in this paper. Titus[12] believed that a rising leukocyte count and a sedimentation rate which is becoming accelerated are indications for immediate surgery. The leukocyte counts are shown in Table V.

TABLE IV. CLINICAL OBSERVATIONS

CLINICAL OBSERVATIONS	LOCALIZED TO THE APPENDIX (28 CASES)	WITH PERITONITIS (17 CASES)	TOTAL (45 CASES)
A. Fever.—			
1. Below 99° F.	7 (25.0%)	3 (17.6%)	10 (22.2%)
2. 99°-100.4° F.	21 (75.0%)	11 (64.8%)	32 (71.1%)
3. 100.5°-102° F.	0	3 (17.6%)	3 (06.7%)
4. Above 102° F.	0	0	0
B. Abdominal Findings.—			
1. Right lower quadrant tenderness	28 (100.0%)	17 (100.0%)	45 (100.0%)
2. Muscle spasm	9 (67.8%)	11 (64.8%)	30 (66.6%)
3. Distention	2 (07.1%)	3 (17.6%)	5 (29.5%)

TABLE V. LABORATORY FINDINGS

LABORATORY FINDINGS	LOCALIZED TO THE APPENDIX (24* CASES)	WITH PERITONITIS (17 CASES)	TOTAL (41* CASES)
A. White Blood Cell Count.—			
1. Below 10,000	7 (29.2%)	0	7 (17.0%)
2. 10,000-20,000	17 (70.8%)	14 (82.3%)	31 (75.6%)
3. Above 20,000	0	3 (17.7%)	3 (07.4%)
B. Polymorphonuclear Leukocytes.—			
Above 80%	15 (62.5%)	15 (88.2%)	30 (73.1%)
C. Nonfilamentous Polymorphonuclear Leukocytes.—			
Above 10%	12 (50.0%)	12 (70.5%)	24 (58.5%)

*No blood count done in 4 cases.

If a patient had two or more of the subjective symptoms listed in Table II, *C*, the history was considered typical. In our series 33, or 73.3 per cent, were considered to be typical and 12, or 26.7 per cent, atypical. Of the atypical cases 11, or 91.6 per cent, occurred after the third month of pregnancy.

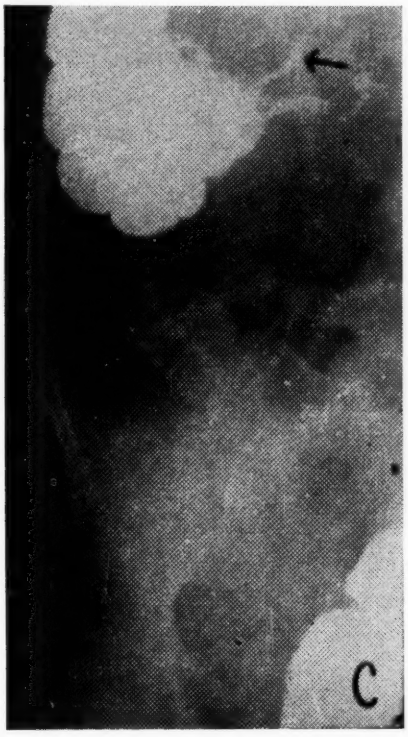

Fig. 4.—End of the eighth month. The cecum and appendix are displaced still higher above the iliac crest. (From Baer, Reis, and Arens.[4])

The differential diagnosis of acute appendicitis during the three trimesters should include the following:

1. During the first trimester:
   a. Ectopic pregnancy
   b. Salpingitis
   c. Early abortion
   d. Ovarian tumors
   e. Kidney or ureter stones
2. During the second trimester: the above plus
   a. Nephritis and pyelitis
   b. Gall bladder disease
   c. Intestinal obstruction
   d. Peptic ulcer
   e. Mesenteric lymphadenitis and thrombi
   f. Carbuncle of kidney
3. During the third trimester: the above plus
   a. Premature labor
   b. Placenta previa
   c. Abruptio placentae
   d. Eclampsia

TABLE VI. OPERATION

OPERATION	LOCALIZED TO THE APPENDIX (28 CASES)	WITH PERITONITIS (15* CASES)	TOTAL (43* CASES)
A. Anesthesia.—			
1. General			35 (81.4%)
2. Spinal			8 (18.6%)
B. Incision.—			
1. McBurney's			10 (23.2%)
2. Midline			6 (13.9%)
3. Right rectus			24 (55.8%)
4. Other			3 (07.1%)
C. Mobility of Appendix.—			
1. Freely movable	14 (50.0%)	4 (26.6%)	18 (41.9%)
2. Rectrocecal	11 (39.2%)	5 (33.3%)	25 (58.1%)
3. Fixed by adhesions	3 (10.8%)	6 (40.1%)	

*Two cases not operated upon.

TABLE VII. COURSE OF PREGNANCY DURING THE ACUTE PHASE OF THE DISEASE WHILE IN THE HOSPITAL

EXTENT OF INFECTION	UNDELIVERED			DELIVERED			MORTALITY	
	UNEVENTFUL	THREATENED ABORTION	DEATH IN UTERO	ABORTION	PREMATURE LABOR	FULL-TERM LABOR	MATERNAL	FETAL
Localized to appendix	25	2	0	0	1	0		1 (3.5%)
	96.4%			3.5%				
With peritonitis	9	2	1	2	1	2	1 (5.8%)	4 (29.4%)
	64.7%			29.4%				
Total	38 (84.5%)		1 (2.2%)	6 (13.3%)			1 (2.2%)	5 (11.1%)

Abortion and Premature Labor

Statistics vary from 2 to 26 per cent. These complications are more common when the disease has spread beyond the appendix (Table VII). During the acute phase of the disease, before the patient left the hospital, the abortion and premature rate was 13.3 per cent. The subsequent course of the pregnancy after leaving the hospital was followed in all cases (Table VIII). In this group the fetal loss amounted to 13.1 per cent.

TABLE VIII. FOLLOW-UP STUDY OF THE SUBSEQUENT COURSE OF PREGNANCY IN THE 38 UNDELIVERED PATIENTS

EXTENT OF INFECTION	KNOWN TO HAVE DELIVERED					
	ABORTION		PREMATURE			
	SPONTANEOUS	MISSED	UNCOMPLICATED	COMPLICATED	FULL TERM	FETAL LOSS
Localized to appendix	1	1	0	1*	24 (89.9%)	3* (11.1%)
	11.1%					
With peritonitis	0	0	2	0	9 (81.9%)	2 (18.1%)
	18.1%					
Total	5 (13.1%)				33 (86.9%)	5 (13.1%)

*Fetal loss due to placenta previa at eight months included.

Fetal Mortality

The fetal mortality has been reported by Meiling[6] as 34.6 per cent. In our series the fetal loss during the acute phase of the illness was 13.3 per cent. In the breakdown of our statistics, we found that when the disease was limited to the appendix, the fetal loss was 3.5 per cent. When the disease had spread beyond the confines of the appendix, the mortality increased to 29.4 per cent. Thirty-eight patients delivered after leaving the hospital. In this group the fetal loss was 11.1 per cent when the disease was limited to the appendix, and 18.1 per cent when peritonitis was present. The over-all fetal loss in this group was 13.1 per cent (Table VIII). The over-all fetal loss for both immediate and late cases was 20.4 per cent; when the disease was limited to the appendix, 11.1 per cent; with peritonitis 35.2 per cent (Table IX).

TABLE IX. FETAL MORTALITY

EXTENT OF INFECTION	WHILE IN HOSPITAL (45 CASES)	AFTER DISCHARGE (37 CASES)*	TOTAL (44 CASES)*
Localized to appendix	1 in 28 (3.5%)	2 in 26 (7.6%)	3 in 27 (11.1%)
With peritonitis	4 in 17 (29.4%)	2 in 11 (18.1%)	6 in 17 (35.2%)
Total	5 in 45 (11.1%)	4 in 37 (10.8%)	9 in 44 (20.4%)

*Fetal loss due to placenta previa in eighth month not included.

Maternal Mortality

The maternal mortality is dependent upon the duration of the infection and the period of gestation. After the seventh month of pregnancy, walling off of the infection is unlikely, and widespread involvement of the peritoneal cavity is a great possibility. Mussey[7, 8] reports no deaths in 26 cases; but in another series of 122 cases, he reports 2 deaths, one in the sixth and one in the seventh months. Baer[4] reports no deaths in 28 cases, and Meiling[6] 2 deaths in 26 cases. Both of Meiling's deaths occurred during the ninth month. One patient was operated upon with a diagnosis of perinephritic abscess and at operation the abscess, in the region of the right kidney, was found to be due to a perforated appendix. There was one maternal death in our series. Briefly the history of this case is as follows:

A 19-year-old gravida i, para 0, was admitted to the hospital on April 24, 1947, with a chief complaint of backache of 24 hours' duration. The backache was chiefly on the right side with some radiation of pain to the right flank and thigh. She was first seen in the medical outpatient clinic one month previously with acute bronchitis. At that time the period of gestation was estimated to be 6 months.

Admitting physical examination revealed: temperature 99° F., pulse 88, respirations 20, blood pressure 115/75; clear lung fields; systolic murmur at the pulmonary area, regular rhythm; height of pregnant fundus, 3 fingerbreadths below the xyphoid process; fetal heart rate 140; no varicosities or edema. External pelvic measurements were normal except for the biischial diameter of 6 to 7 cm. Physical examination was negative, except for slight tenderness on pressure in the right costovertebral angle.

She was ambulatory on admission, and in no acute distress. A voided urine specimen obtained soon after admission showed specific gravity 1.016, negative for albumin and sugar, with occasional pus cells. In the late afternoon of the following day, April 25, she complained of persistent backache with occasional cramplike pains. Catheterized urine revealed the same picture as on the previous day, except for a slight trace of sugar and positive staphylococcus culture. A diagnosis of pyelitis was made and antibiotic therapy instituted. Her condition remained stationary for the next 48 hours. The pain in the right costovertebral angle then became more pronounced and radiated along the course of the ureter. No abdominal tenderness or rigidity was noted. A diagnosis of appendicitis was considered.

In the early morning of April 27 (60 hours after admission), her pains became more severe and extended up to the lower right side of the chest and were aggravated with breathing. She was dyspneic and appeared ashen colored, with respirations of 40, pulse 96, and temperature 101° F. Dullness at the right base and axilla, with decreased breath sounds and vocal fremitus, and friction rub were found on chest examination. The abdomen was described as distended and tense. X-ray of the chest taken later in the morning exhibited reduced intrathoracic volume due to increased intra-abdominal pressure and a bronchopneumonic infiltration in the right lower lobe. She was placed in an oxygen tent. The dosage of penicillin was increased, and supportive intravenous therapy was instituted.

In spite of intensive therapy her condition became progressively worse. A diagnosis of subphrenic abscess with extension to the right chest and spreading peritonitis was made. She died 7 days after admission. Fetal heart tones were not heard for 24 hours before death.

Medical, urological, surgical and obstetrical consultations were obtained throughout her course of illness.

The postmortem pathological diagnosis was: 7½ months' uterine pregnancy, undelivered; acute purulent appendicitis and periappendicitis with appendiceal abscess anterior to right kidney; right subphrenic abscess; right fibrinopurulent pleurisy with effusion; pulmonary edema and congestion; atelectasis right lower lobe; acute tracheitis and bronchitis; acute fibrinopurulent pericarditis; acute pyelitis, bilateral.

In retrospect, it is our opinion that this patient probably had a ruptured appendix with perinephritic abscess when seen in the medical clinic three weeks before admission to the hospital.

The history of the second nonoperative case is as follows:

Mrs. B. R., a 22-year-old white gravida iii, para ii, was admitted in the evening of March 15, 1946, with the history of irregular, laborlike lower abdominal pains and persistent right lower quadrant and flank pains. Her last menstrual period was not accurately known, but was thought to have been in the latter part of July, 1945. Her prenatal course had been uneventful. The physical examination was essentially negative, except for low-grade fever (99.8° F.), and normal pregnancy which was clinically full term. On rectal examination, the cervix was dilated 2 cm.; the presenting part (cephalic) was at minus 1 station, and the membranes were intact. Shortly after admission, the intermittent mild uterine contractions subsided; however, the right lower quadrant and flank pains persisted. Tentatively, a diagnosis of pyelitis of pregnancy was made, and penicillin therapy, 50,000 units immediately, followed by 30,000 units every 3 hours, was started.

On the following day she continued to complain of right lower quadrant pain which was associated with pain in the right thigh. A catheterized urine specimen was negative. The blood study revealed moderate leukocytosis of 12,800 with 87 per cent polymorphonuclear cells, 11 per cent nonfilamented. Twenty-four hours after admission, her condition suddenly became worse. The right lower quadrant pain persisted and she began to complain of epigastric pain, vomited twice, and perspired profusely. Her temperature rose to 101.2° F. On the morning of March 17, she appeared acutely ill and toxic. Examination showed normal chest findings, but the abdominal examination for the first time revealed moderate gaseous distention, moderate-to-acute tenderness in the right flank and over McBurney's point. There was no muscle rigidty and no intestinal persistalsis. A diagnosis of ruptured appendix was

made. The patient was immediately placed on an intensive, conservative, nonoperative regimen, because her poor condition seemed to contraindicate surgery. The penicillin was increased to 100,000 units intramuscularly every 3 hours; intravenous fluids were instituted and she was placed in semi-Fowler's position. On the same evening she went into active labor and spontaneously delivered a full-term living male infant. The third stage was uneventful. Immediately post partum her general condition was poor. Her temperature was 102° F.; she continued to have right lower quadrant pains, perspired profusely, and was having respiratory difficulty. Her postpartum course was stormy for the first two days. Beginning on the fourth postpartum day she began to improve rapidly. The penicillin was reduced to 75,000 units every 3 hours, and she was able to tolerate her foods fairly well. On the seventh postpartum day, the intravenous fluids were discontinued, and the penicillin was reduced to 50,000 units. On the ninth postpartum day she had no complaints and all medications were discontinued. Her temperature returned to normal on the fourth postpartum day. A total of 5,550,000 units of penicillin were given over eleven days. The leukocyte count fell to 7,350 on the third postpartum day. She was discharged from the hospital on the eleventh postpartum day. Appendectomy was done some weeks later and the diagnosis of previous rupture confirmed.

Treatment of Acute Appendicitis

1. Prophylactic.—All pregnant patients should be watched closely for signs and symptoms of acute appendicitis. This is especially true during the second and third trimesters, and if there is a history of previous infection. It is our opinion that when the diagnosis of appendicitis has been made, appendectomy should be done regardless of the age of the patient, whether married or single, whether pregnant or not.

2. During First Six Months.—Appendectomy is the procedure of choice. Maternal mortality is not increased and the diagnosis is not difficult.

3. During Last Trimester.—Some believe that, in the presence of acute appendicitis with perforation and generalized peritonitis, cesarean section should precede the appendectomy. Others believe that cesarean section should be done only in the rare case. We favor appendectomy only, regardless of the stage of gestation, and would add that interference with the pregnancy is a violation of basic surgical principles.

We believe that, during the prenatal period, the obstetrician should watch for signs and symptoms of appendicitis, especially in those patients who give a history of previous attacks. During the first trimester this is not difficult. When the subjective symptoms are atypical the diagnosis may be delayed, especially during the last trimester when the interpretation of signs and symptoms may be more difficult. When in doubt, and regardless of the period of gestation, we believe the operation is indicated.

When the appendix has been perforated more than 8 hours, and there is evidence of spreading peritonitis, it appears that conservative management with antibiotics, penicillin, and streptomycin is desirable. Following rupture of the appendix, local peritonitis follows. Continued leakage leads to generalized peritonitis with invasion of the peritoneum and lymphatics. The infection then becomes systemic and operation with or without drainage will offer the patient nothing. If such a patient is operated upon and drainage instituted, the drain soon becomes walled off with omentum and intestines. In generalized peritonitis it is impossible to drain the entire peritoneal cavity. George Crile, Jr.,[13]

has been successful in the treatment of peritonitis with penicillin. He favors the use of 100,000 units of penicillin every 2 hours until the patient shows definite evidence of improvement. The dosage is then decreased to 50,000 units. Kennedy, McCadie, and Arminski[14] reported a series of 80 cases of peritonitis treated with penicillin. They favor a smaller dosage of penicillin (50,000 units), but state that better results are observed when these smaller dosages are combined with sulfonamides. If favorable results are obtained in the treatment of spreading peritonitis due to ruptured appendices with large doses of penicillin in nongravid patients, we see no reason why penicillin should not be employed in the gravid patient. It is our belief, however, that surgical intervention, regardless of the stage of gestation, is the treatment of choice.

Our cases of acute appendicitis in pregnancy were divided into two five-year periods. The first five-year period shows an over-all fetal loss of 40.9 per cent in 22 cases, as shown in Table X. (Fetal loss in the eighth month due to pla-

TABLE X. FETAL LOSS, 1943-1947, INCLUSIVE

ACUTE APPENDICITIS IN PREGNANCY	ACUTE PHASE (23 CASES)	LATE PHASE (18 CASES)*	TOTAL (22 CASES)*
Localized to appendix	1 in 14 (7.2%)	3 in 13 (23.1%)	4 in 13 (30.7%)
With peritonitis	3 in 9 (33.3%)	2 in 5 (40.0%)	5 in 9 (55.6%)
Total	4 in 23 (17.4%)	5 in 18 (27.7%)	9 in 22 (40.9%)

*Fetal loss in eighth month due to placenta previa not included.

TABLE XI. FETAL LOSS, 1948-1952, INCLUSIVE

ACUTE APPENDICITIS IN PREGNANCY	ACUTE PHASE (22 CASES)	LATE PHASE (21 CASES)	TOTAL (22 CASES)
Localized to appendix	0 in 14 (0%)	0 in 14 (0%)	0 in 14 (0%)
With peritonitis	1 in 8 (12.2%)	0 in 7 (0%)	1 in 8 (12.2%)
Total	1 in 22 (4.5%)	0 in 21 (0%)	1 in 22 (4.5%)

TABLE XII. DURATION OF SYMPTOMS, 1943-1947

DURATION OF SYMPTOMS 1943-1947 (21 CASES OPERATED UPON)	LOCALIZED TO APPENDIX	WITH PERITONITIS	TOTAL
1. 24 hours or less	7 (50.0%)	2 (28.6%)	9 (42.9%)
2. 25-71 hours	5 (35.7%)	4 (57.1%)	9 (42.9%)
3. More than 71 hours	2 (14.3%)	1 (14.3%)	3 (14.2%)

TABLE XIII. DURATION OF SYMPTOMS, 1948-1952

DURATION OF SYMPTOMS 1948-1952 (22 CASES OPERATED UPON)	LOCALIZED TO APPENDIX	WITH PERITONITIS	TOTAL
1. 24 hours or less	13 (92.8%)	6 (75.0%)	19 (86.3%)
2. 25-71 hours	1 (07.2%)	1 (12.5%)	2 (09.1%)
3. More than 71 hours	0	1 (12.5%)	1 (04.6%)

centa previa is not included.) In the second five-year period, 1948-1952, inclusive, the fetal loss amounted to 4.5 per cent in 22 cases (Table XI). We would like to attribute this increase in fetal salvage to early diagnosis. In the first 5-year period, 42.9 per cent of the cases were operated upon within 24 hours (Table XII), while during the last five-year period 86.3 per cent of the patients were subjected to surgery within 24 hours (Table XIII). The liberal use of antibiotics and sedatives during the immediate postoperative period has also contributed to the low fetal loss. We have had no experience with progesterone postoperatively in these cases.

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Discussion

DR. GEORGE WULFF, JR., St. Louis, Mo.—Acute appendicitis complicating pregnancy is admittedly an infrequent clinical picture confronting the average obstetrician. Although each of us has seen or heard of a case occasionally, ability to draw conclusions from one's personal experience with this condition is practically impossible. This obstetrical emergency occurs with an incidence of 0.1 per cent or less, as reported by various investigators.

We are especially indebted, therefore, to Drs. Hoffman and Suzuki for their prolonged study of this subject. Their paper presented this morning provides the largest series of cases of this disease reported in the current literature, and merits the close scrutiny of all of us in the obstetrical specialty.

An attempt was made to compare the author's statistics with those of our own obstetrical service at Washington University. This was complicated, however, by the fact that surgery in acute cases is not performed in St. Louis Maternity Hospital, but in the adjacent Barnes Hospital. Some of those patients operated upon at Barnes undoubtedly were delivered at other hospitals; therefore to have assessed these surgical procedures against the deliveries at Maternity Hospital would have been misleading.

Because of the conversion of our records to microfilm and the I.B.M. system, only three years were available for comparison: 1949, 1950, and 1951. During these years there were 10,317 deliveries, and there were 11 patients operated upon for the clinical diagnosis of acute appendicitis. These cases occurred in an incidence, therefore, of 0.106 per cent (ratio of 1 case to 938 deliveries) which is almost identical with that presented here this morning, and with that of other reported series. However, when we exclude the 4 patients whose deliveries could not be positively traced to Maternity Hospital, the remaining 7 cases represent an incidence of only 0.068 per cent (ratio of 1 case to 1,474 deliveries). A further breakdown of these cases showed 6 to be pathologically proved acute appendicitis.

Only one of our 7 cases resulted in premature termination of the pregnancy and that was an acute case in which the patient aborted a five-month stillborn fetus seven days after

the appendectomy. This represents a fetal loss of 14 per cent, as all of the other 6 patients were delivered uneventfully at term.

There was no maternal death in our group and the cases were almost equally divided among the three trimesters of pregnancy. In discussing the stage of pregnancy, however, it is well to emphasize the statement in the paper you have just heard, that after the seventh month of pregnancy, walling off of the infection is unlikely, and widespread involvement of the peritoneal cavity is a great possibility. Actually, this is a very modest understatement. The increasing dangers which confront us as pregnancy approaches term are serious ones and must be appreciated. Because of the irritability of the uterus and its intermittent contractions, abscess formation takes place much less frequently. The obstetrician is prone to procrastinate in this diagnosis at a time when procrastination multiples the dangers many fold.

The mortality of acute appendicitis is the mortality of delay. If the attending physician constantly bears this fact in mind, he will be less likely to hesitate in order to make what he feels is an "ironclad" preoperative diagnosis.

A study of this nature always stimulates interest in related subjects. It does not seem justified in this connection to eliminate the immediate postpartum period from such a study. Although the fetal outcome is not affected, the maternal morbidity and mortality can be as great just after birth as before. In fact, the involuting uterus and its contractions can mask the symptoms of acute appendicitis very tragically as some of us have had the misfortune to learn. The localization of an inflammatory process is interfered with tremendously. The disastrous consequences thus occurring should keep the possibility of this complication of the puerperium ever present in our minds. It would certainly be worth while for the authors to discuss this phase in the final publication of their work.

If we review their work carefully and heed their advice, we too shall be on the alert for this complication and, if the appendix is suspected, operate!

DR. HOFFMAN (Closing).—We have made some studies of acute appendicitis developing during labor and the puerperium. The series is not large enough to include in this study, and we hope we will be able to make that a separate study.

I certainly agree with Dr. Wulff that widespread involvement of the peritoneal cavity occurs during the last trimester after appendix rupture is putting it rather modestly. The thing we want to emphasize, I believe, is that the diagnosis during the last trimester may be a very difficult one to make, and unless one keeps it constantly in mind there will be people with acute appendicitis who are thought to have pyelitis.

It is interesting to note in our series that even though the fetal loss was less in the second five-year series, the number of patients operated on with a preoperative or admitting diagnosis of acute appendicitis was the same, and the number of chronic cases was no greater than in the first five-year series.

I would like to make one statement for which I have no basis in fact statistically or otherwise; it is just an intuition, if you wish to call it that. I have the feeling, as we go through the series and carry it on for perhaps another five or ten years, that we may find that women develop appendicitis during pregnancy purely as a coincidence, and that a history of previous infection and the displacement of the appendix may mean nothing in the production of acute appendicitis during pregnancy.

URINARY CALCULI IN PREGNANCY*

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THE occurrence of a ureteral calculus in a recent pregnant patient has stimulated a study of the general subject of urinary calculi in pregnancy. Established therapeutic routine is not well defined and it is hoped to develop a more specific approach.

The textbooks of obstetrics and gynecology and the literature in general reveal a paucity of information on this subject and the English literature of the past twenty years contains only scattered references to this problem. Although the incidence of this complication of pregnancy is low, there is little information available for any physician faced with this acute and often urgent complication.

Following a résumé of the English literature of the past twenty years, a survey was made of the obstetrical records of the Evanston Hospital Association for the past ten years to find similar cases and to re-evaluate this syndrome.

Etiology

There are several well-known theories of stone formation. These are not pertinent to this discussion. However, it is well established "that more than 85 per cent of pregnant women have demonstrable changes in the ureteral tone and anatomic character of the upper urinary tract."[1] The stasis thus produced, together with the resultant urinary tract infection, may lead to formation of calculi. The incidence of urinary tract infection in pregnancy varies in reported series "from as low as 0.6 per cent to as high as 16.3 per cent; the majority placing it between 1 and 2½ per cent."[3]

In addition, pregnancy causes alterations in mineral metabolism and there may be responsible endocrine factors; for instance, experimentally high doses of estrogen increase the incidence of calculus formation in mice.[1] Why, therefore, is the incidence so low in spite of these pregnancy factors which would seem to invite stone formation? There are several possible answers:

1. The blood calcium and phosphorus are not changed remarkably in spite of definite changes in mineral requirements in pregnancy.

2. The average age at which urinary calculi occur is considerably higher than the average age of pregnant women. Inasmuch as time is considered to be a factor in stone formation, this would weigh against the more frequent formation of calculi during the childbearing years.

*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 6, and 7, 1953.

3. It is probably safe to say that the average pregnancy diet of today has a higher vitamin content than the normal diet of women in general. This would seem to rule out the vitamin deficiency theory.

4. The physiological dilatation produces a paradoxical effect, in that there is increased stasis but less mechanical obstruction.

5. Finally, and most important, the stasis with or without infection in any one pregnancy is presumably of too short a duration to allow for calculus formation.

Incidence

It is not usually possible to distinguish the urinary stone which antedated the gestation from one acquired in pregnancy. "The latter class of cases is probably greater than the statistics show since there is a considerable group of patients in whom the stone is discovered only after a few months' investigation of persistent infections."[3]

Everett states that an exact estimate of the incidence of calculous disease among the general population is difficult or impossible to determine, partly because of marked geographic, geologic, and climatic influences.[9]

Arnell and Getzoff[1] report an incidence of 1:525 with a 2:5 to 1 ratio of males to females. The incidence in nonpregnant females was 1:1,100. In the same period of hospital admissions studied they report a 1:820 incidence in pregnancy and compare this to a reported incidence at the Chicago Lying-in Hospital of calculi in pregnancy of 1:900. They conclude that the frequency of calculous disease of the upper urinary tract associated with pregnancy is somewhat greater than in nonpregnant women (average 1:852 and 1:1,100) but not as great as in the male (1:320).[1] Another report[9] states an incidence varying from 1:1,000 to 1:2,500 in pregnancy, and still a third[2] reports an incidence of zero in 15,000 obstetric admissions.

The incidence in the white race is reported to be greater than in the Negro.[9] It is greater in multiparas than in primiparas.[9] The same study reports an average age of 28 years and a parity average of 3.8, with an average duration of gestation at the onset of symptoms of 24 weeks. Ureteral calculi were twice as common as renal calculi.

From Nov. 1, 1940, to Nov. 1, 1950, there were 13,484 obstetrical admissions to the Evanston Hospital, not including 1,207 abortions. In these 13,484 patients there were 94 recorded urinary complications, not including bladder retention or transient inability to void, an incidence of 0.6 per cent, or one in every 143 cases. This low figure does not account for patients treated at home and reflects the improved control of urinary tract infection by chemotherapy and/or antibiotics. There were 6 patients with a diagnosis of calculus, an incidence of 1 in 2,247 deliveries.

Case Reports

The six cases which occurred at the Evanston Hospital and one at the Highland Park Hospital are briefly summarized as follows:

CASE 1.—A 32-year-old gravida iii, para ii, was admitted when four and one-half months pregnant with a diagnosis of stone in the left renal pelvis. She gave a history of a renal stone four years previously. An immediate nephrectomy was performed. The postoperative result was good and the patient carried the pregnancy uneventfully to term.

CASE 2.—A 31-year-old gravida iii, para ii, with no significant past history, was admitted six and one-half months pregnant with a calculus in the middle third of the left ureter. No attempt was made to remove the stone because there was no ureteral obstruction. The calculus was passed spontaneously in the postpartum period.

CASE 3.—A 27-year-old gravida ii, para i, with no history of stone, was admitted in the fourth month of pregnancy with severe ureteral colic. The stone was passed spontaneously while in the hospital and the patient carried to term without further complications.

CASE 4.—A 29-year-old gravida iv, para iii, with no history of stone, was admitted in the eighth month of pregnancy with a calculus in the lower third of the ureter. Treatment was symptomatic and the stone passed spontaneously without much delay. The patient carried the pregnancy to term.

CASE 5.—A 28-year-old gravida ii, para i, was admitted at term with a diagnosis of calculus in the left renal pelvis. This kidney had a double pelvis. No treatment was given and the calculus was still present at the time of her next delivery, thirteen months later.

CASE 6.—A 24-year-old gravida iii, para ii, had ureteral colic following delivery and passed a small calculus on the fourth postpartum day.

CASE 7.—This patient was delivered at the Highland Park Hospital. The patient, a gravida iv, para ii, was admitted to the hospital four weeks from term with agonizing left ureteral colic. X-ray examination demonstrated a left ureteral stone with obstruction. Because symptomatic therapy was of no avail, labor was induced by artificial rupture of the membranes and the administration of Pitocin intravenously. The patient was delivered of a normal 5 pound, 2 ounce, female infant after a two and one-half hour labor. On the third postpartum day the calculus was passed spontaneously.

Symptoms and Findings

The symptoms and findings in the order of frequency, as listed by Arnell and Getzoff,[1] are costovertebral pain and tenderness, abdominal pain and tenderness, fever, pyuria, hematuria, nausea and vomiting, frequency of urination with dysuria, chills, and muscular spasm. This corresponds with the findings in our own patients.

Comment

Some authors state that the diagnosis is difficult. This is not easy to understand. The differential diagnosis in pregnancy includes in the order of frequency: pyelitis, pyelonephritis, acute appendicitis, cholecystitis, a general gall bladder symptom-complex, and extrauterine pregnancy.

The identification of renal calculi in pregnancy should not be difficult if the clinical features are kept in mind, and if proper diagnostic procedures are instituted. Any patient with severe costovertebral pain and tenderness or severe abdominal pain and tenderness accompanied by fever, nausea and vomiting, must be suspected of having a stone with associated infection. If, in addition, the patient complains of urination with burning, and intermittent

chills, the urinary origin of the disease process becomes more apparent. Urine specimens must be examined for pyuria and hematuria and must be obtained by catheter to have critical diagnostic significance. Exploratory scout films after suitable preparation are possible and intravenous pyelograms are most often diagnostic. The most commonly confused syndrome, which is also much more frequent, is pyelocystitis in pregnancy.

Therapy should be different for each of the three trimesters of pregnancy. It seems to be well established that active interference is the treatment of choice in the first trimester unless the condition is latent and is producing no obstruction.[3, 8, 9] Such active treatment should be cystoscopic manipulation whenever possible. Nephrotomy or ureterotomy is necessary when the ureteral approach fails. Expectant therapy at this time carries the risk of serious complications at a later period in pregnancy when surgery is not only more difficult but many times more dangerous, and often impossible. The general principle, therefore, that obtains at this time is that surgical removal of both renal and ureteral stones should be carried out in the first trimester whenever there is obstruction. In most instances such therapy will not disturb the pregnancy.

In the second trimester of pregnancy the kidney is still available to surgical attack and renal calculi may be removed safely when necessary; that is, when the symptoms are severe and/or obstructive damage is being done to the kidney. To a lesser extent, this is also true of calculi located in the upper one-half of the ureter. The lower one-half of the ureter at this time becomes progressively less accessible and, furthermore, surgical intervention is dangerous at this time because of the tremendous enlargement of the related blood vessels. If an obstructing stone is not passed spontaneously within a short period after the onset of symptoms and, particularly, if expectant therapy is of no avail and the obstruction is complete or nearly complete, some intervention is mandatory. These cases should then be grouped with similar cases in the third trimester of pregnancy as far as therapy is concerned.

In the third trimester of pregnancy the urinary tract should not be subjected to surgery for calculus, with the exception of a lifesaving nephrostomy.[2, 9] The urinary tract is not often even accessible for safe cystoscopic manipulation and, therefore, a ureteral attack on the stone is contraindicated. Again, if conservative and symptomatic therapy does not ameliorate the severe symptoms and if the patient has any degree of obstruction which is likely to cause permanent damage to the kidney, interference becomes imperative. The safest method and the one most likely to be successful appears to be evacuation of the uterus.[3]

In Case 7, successful premature induction of labor was followed by spontaneous passage of the stone. A similar outcome occurred in the postpartum period in Case 2. In the event that this happy result does not follow within a reasonable period of time, the urinary tract, with the progressive daily involution of pregnancy changes, will rapidly become easily and safely accessible to cystoscopic or surgical approach. The future health and longevity of the mother may rarely require the sacrifice of a previable baby.

An interesting by-product of this study was the confirmation that urinary tract infection is no longer a serious complication of pregnancy. This improvement is due to the use of chemotherapy and antibiotics. It was demonstrated further that too infrequent use is being made of culture and sensitivity tests in order that specific therapy may be used. Our routine is to catheterize under aseptic conditions all patients with urinary complications and send the specimens to the laboratory for culture, organism identification, and sensitivity tests with the usual sulfonamides and antibiotics. One need not wait for the laboratory report to initiate therapy but it is essential to have a specific weapon available if the patient does not respond to what is of necessity at the outset blind therapy.

Summary

1. Although renal and ureteral colic does not constitute a common complication of pregnancy, it occurs in some reported series more often than in the nonpregnant woman of a similar age group.

2. Urinary calculus can be a formidable complication requiring the most careful consideration on the part of the obstetrician and consulting urologist.

3. The clinical features are classical and the diagnosis will not be difficult if the clinician is alert to the possibility of this condition.

4. Six cases representing an incidence of 0.04 per cent or one in every 2,247 obstetrical admissions to the Evanston Hospital are presented, and a seventh case is reported from the Highland Park Hospital.

5. We agree with previous authors who recommend surgical removal early in pregnancy and conservative treatment in the third trimester. However, we would like to emphasize that where conservative therapy fails and there is danger of permanent damage to the kidney, the pregnancy should be terminated. When this is done there seems to be reasonable expectation of spontaneous passage of the calculus. Failing this, surgical intervention then becomes possible within a short period of time.

6. Advantage is not being taken of the available laboratory procedures for more specific treatment of urinary tract infections.

7. The advent of chemotherapy and antibiotics has resulted in a lowered incidence of urinary tract infection without stone or other organic complications during pregnancy.

Conclusions

1. The incidence of urinary calculi in pregnancy at the Evanston Hospital, from 1940 to 1950, was 0.04 per cent, or 1 in every 2,247 obstetric admissions.

2. The treatment of obstructing ureteral stone during the first trimester of pregnancy is removal by cystoscopic manipulation or surgery.

3. Obstructing ureteral stone in late pregnancy may require termination of the pregnancy in order to permit spontaneous passage of the stone. When this does not occur manipulative or surgical removal has been made possible and safe.

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Medical Arts Building

Discussion

DR. E. K. BLEWETT, Austin, Texas.—Dr. Solomon has presented an excellent review of this rather rare complication of urolithiasis in pregnancy. In the treatment of this complication, it is wise to follow the general dictum to "treat the disease and ignore the pregnancy."

The management must be individualized and close cooperation between the urologist and obstetrician is essential. We agree with Dr. Solomon that if the complicating ureteral or renal stone is asymptomatic and not causing blockage conservatism is preferable. After pregnancy the stone should be removed. In the presence of infection without urinary blockage appropriate chemotherapy should be instituted. However, we cannot agree with Dr. Solomon that ureteral manipulation and renal and ureteral surgery should never be performed during the last half of a pregnancy. In the presence of complete urinary blockage, and/or intractable pain, and/or severe infection, appropriate surgical measures should be instituted if improvement is not obtained in a reasonable length of time under conservative management. Our experience has led us to believe that cystoscopic examinations and ureteral catheter manipulations may be carried out quite safely at any stage of pregnancy for the treatment of selected urological conditions.

In the presence of blockage by a renal stone, it is necessary that drainage be established by an inlying ureteral catheter, pyelonephrotomy, or even a nephrostomy. Sometimes a small renal stone will pass spontaneously after ureteral catheter manipulation. A nephrolithotomy, pyelolithotomy, or even a nephrectomy has on occasion been necessary. In the presence of a ureteral stone causing complete blockage, drainage can be instituted by means of a ureteral catheter passed proximal to the site of the obstruction. Sometimes the stone will be dislodged by the ureteral manipulation and it will pass spontaneously. If, however, the catheter cannot be passed by the site of the obstruction, drainage may be accomplished by a ureterolithotomy, or if the stone is in the lower third of the ureter during the last trimester of the pregnancy, a ureterostomy may be performed proximal to the obstruction and drainage instituted by an indwelling T tube in the ureter and drainage established until the pregnancy can be carried to viability and terminated by appropriate means.

DR. GERALD W. GUSTAFSON, Indianapolis, Ind.—I think it might be worth while also to mention the possibility of difficulties with the symptomless bladder stones that we occasionally see.

A few years ago on my service at Indianapolis General Hospital, in a patient at term, in labor, we found that there was a bladder stone of about 5 cm. in diameter. The interns had felt that it was some abnormal presenting part at the time. I managed to deliver the patient from below with forceps, as she had a fairly good-sized pelvis, but I can think of the possibility that a bladder stone might be of sufficient size even to block the birth canal. It certainly would be important to have the diagnosis made beforehand.

In the case that I mentioned, the stone had to be removed by cystotomy later on. The urologist found it impossible to crush it, and operation had to be resorted to.

DR. SOLOMON (Closing).—I agree that it is possible to make a cystoscopic approach to the ureters any time in pregnancy, even at term. All urologists say, "Of course we can do it." They are all very unhappy when they are faced with the problem.

This procedure is most often a failure, besides subjecting the patient to an enormous amount of discomfort and the ureters to a fair amount of trauma. We do agree that the pregnancy is of secondary importance, and it is merely a difference in philosophy as to how we approach the end result that the pregnancy is of secondary importance.

I happen to belong to a school that believes that labor can be induced in any patient, almost without exception, with a proper approach.

REMOVAL OF 184 POUND OVARIAN TUMOR, AND OBSERVATIONS REGARDING SPLANCHNIC SHOCK*

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THE sudden release of acute intra-abdominal pressure has been said at times to cause the appearance of shock, commonly called splanchnic shock, and it is most commonly reported to follow catheterization of a distended bladder, the removal of large amounts of ascitic fluid, or large abdominal tumors. Unfortunately, there is little information in our literature concerning this phenomenon.

The ovarian tumor presented in this paper has been found, following an extensive review of the literature, to be the thirteenth largest reported and is the largest which has been removed intact. As such, with its comparatively sudden release of acute intra-abdominal pressure, it is felt to offer an exceptional opportunity for observations regarding possible appearance of splanchnic shock.

The possibility of such shock following removal of a large abdominal tumor is felt to represent less of a threat to the patient's future than does repeated tapping and draining. The potential hazards of drainage are quite worthy of consideration. Probably foremost is the inevitable spillage of fluid into the peritoneal cavity, regardless of the size needle which may be used, and the accompanying almost certain dissemination of any malignant cells which may be present. The incidence of intra-abdominal infection is increased with tapping; the tapping of a hemorrhagic-type cyst may well permit serious internal hemorrhage; repeated tappings will increase the number and density of adhesions; and, finally, it is often more technically difficult to remove a collapsed sac than a firm full one. Preliminary tapping and drainage of such a large cyst are felt to be unjustifiable except in extreme cases where pressure upon vital organs is so severe as to preclude surgery in the patient's present physical condition, and relief of pressure is necessary to obtain satisfactory physical status to permit surgical removal. Removal in toto is a primary surgical principle and should not be violated on the basis of size of a tumor alone. A larger tumor merely requires a more generous incision.

The exact etiology of this elusive condition which has been named splanchnic shock is a mystery, and attempts at its reproduction in animals have been made without a satisfactory explanation. Obviously, it is almost impossible to duplicate and maintain such a prolonged rise of intra-abdominal pressure as would be necessary to approximate these comparatively rare curiosities. Ridley,[14] as

*Presented at the joint meeting of the Houston Obstetrical and Gynecological Society and the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5, 1953.

late as 1951, failed to find a ready explanation following experimentation with rabbits. It has been hypothesized that the intra-abdominal veins compressed during abdominal distention might act as a reservoir for the blood otherwise returning to the heart when distention is abruptly released; or that the rapid release of abdominal distention quickly releases the peripheral resistance offered by the partial compression of the abdominal aorta and results in a quick fall in arterial pressure before the unequally distributed blood in the venous system returns to a normal balance. It appears, however, at least following relief of pressure from intra-abdominal tumors, that the explanation is not as mechanically simplified, for we most often note the occasional difficulty some few hours following release of pressure and not at the actual time of release. Thus is suggested an obscure etiology requiring a varying period of time for its maximum effect, perhaps originating within the autonomic nervous system in some manner. The greatest interval of danger seems to be from four to twenty-four hours following release of pressure.

Kehrer,[13] in 1929, reviewed 100 reported cases of ovarian tumors weighing more than 55 pounds. His conclusion was that the greatest danger of postoperative syncope was in the first and second day following operation. Eleven of the 21 recorded operative and postoperative deaths occurred within three days or less. Ten of the 11 occurred within forty-eight hours, 7 within the first twenty-four hours. Two of these 7 deaths took place during the operation, with the other 5 being spread over the first twenty-four hour postoperative period. It is difficult to evaluate the true significance of these results for most of the case reports contain only meager information in all respects.

One would also wonder what change might have been wrought by the use of blood transfusions and modern anesthesia. However, the impression is gained, with this necessarily small series, that the critical period was some hours following operation and not at the time intra-abdominal pressure was released.

In reviewing the 12 cases of ovarian tumors which are larger than the one being here reported the extreme in intra-abdominal pressure is observed.[1-12] One of the 12 patients died prior to any treatment. Another tumor was drained on three consecutive days and the patient died on the fourth day before operation could be accomplished; no shock was mentioned in the case report. The remaining 10 patients were operated upon following drainage, or had drainage at the time of operation. Five patients survived the postoperative period; 3 of these 5 had their first drainage at the time of operation, and 2 had drainage for a varying length of time prior to operation. In only 2 of the 10 cases operated upon was a condition of shock definitely referred to in the report. One tumor was drained two days prior to operation and one was drained at the time of operation; the former patient died. No entity definable as splanchnic shock is noted in these cases. Nearly all of these case reports are very brief and without sufficient details; therefore, no accurate conclusion may be presented. However, again the superficial impression is that there is no advantage derived from prolonged decompression as compared to complete surgery at one sitting.

The treatment of postoperative syncope, or splanchnic shock, if there truly be such an entity due solely to release of intra-abdominal pressure, is the same as for that of any other cause, and may be adequately controlled by foresight and rapid therapeusis if needed. Its infrequent appearance in the face of modern medical therapeutics makes it of secondary importance when compared to the possible long-range complications of each tapping and draining. Prophylactically, following release of acute intra-abdominal pressure, the blood pressure and pulse rate should be checked every fifteen to twenty minutes for the first twenty-four hours and every thirty minutes for the following twenty-four hours, for only by this means could a sudden onset of splanchnic shock be detected.

Case Report

T. C. (Case 2490, U. H. 19462-I), a 44-year-old married Latin-American, gravida v, para iv, was admitted to the hospital on Nov. 7, 1952, with the chief complaint of abdominal enlargement.

The patient had noted the onset of progressive abdominal enlargement about one year previously and had initially believed herself to be pregnant. She was quite emphatic in her denial of any abdominal enlargement or abdominal masses prior to that time. For the past four months she had been confined to her bed by the weight of her abdomen, and required the assistance of four individuals to either turn or sit up in bed. Other than the size of the abdomen, she had few complaints and had an amazingly minimal interference with the essential body functions. A marked weeping edema of the lower extremities had been present for two or three months; also, a marked dyspnea occurred in the supine position but was practically absent in the sitting and lateral positions. The past history was noncontributory.

The last menstrual period was approximately five months previous to admission, the exact date being questionable. The youngest child was 5 years of age.

Physical Examination.—The over-all impression was that of a surprisingly cooperative, emaciated patient somewhat incidentally attached to a huge mass lying in front of and overshadowing her. Dr. Willard Cooke evaluated the situation most admirably when he stated, "She looks like a tangent arising from a circle."

Severe distention caused the skin overlying the abdomen to exhibit a tense, smooth, shiny appearance, beneath which large dilated veins could be seen coursing through the thin subcutaneous tissue. On the right and left sides of the abdomen were decubitus-like ulcers about 25 and 15 cm., respectively, in size. The contour of the abdomen was generally rounded; it was flat to percussion and seemed to contain fluid though no definite fluid wave could be elicited. The waist measurement at the umbilicus was ninety inches (Figs. 1 and 2). Both lower extremities exhibited a 4 plus pitting and weeping edema combined with early ulceration on the lower left anterior tibial region. A pelvic examination was impossible. The blood pressure was 120/80.

Laboratory Results.—A voided urine specimen showed a 1 plus albumin, and a specific gravity of 1.015. The hemoglobin was 7.2 Gm. per 100 ml. of blood, the erythrocyte count 2.27 million per cubic millimeter, and the leukocyte count was 9,300 per cubic millimeter. The fasting blood sugar was 117 mg. per cent, the blood nonprotein nitrogen was 29 mg. per cent; total serum proteins were 5.4 Gm. per cent, albumin 2.8 Gm. per cent, and globulin 2.6 Gm. per cent. The Kahn and Kolmer tests were negative. The arm-to-tongue circulation time was 11 seconds. The venous pressure was 140 mm. of water. The electrocardiogram showed no definite changes. Attempts at x-ray of the chest were unsuccessful. Blood volume studies with radioactive serum albumin prior to transfusion on November 11 revealed plasma volume to be 4,116 c.c., and blood volume to be 6,333 c.c.

The patient was transfused with 1,000 c.c. of whole blood on November 9, 10, 11, and 12.

Operative Procedure.—The operation was performed on November 13 in the left lateral position with cyclopropane and nitrous oxide anesthesia. A right paramedian incision extending from beneath the umbilicus almost to the rib margin was made; the incision was estimated to be three to four feet in length. Moderately firm adhesions between the cyst wall and the peritoneum were encountered but separated without undue difficulty. This incision did not permit delivery of the cyst without its rupture and accordingly it was extended from its approximate mid-portion as a T-shaped incision to the right anterior superior iliac spine. The tumor was found to originate from the left adnexa and was removed intact, thus avoiding spillage of any possible malignant cells. Following excision of 3,700 grams of excess abdominal wall the patient was repositioned into the supine position for a routine and uneventful closure. Blood loss during the operation was minimal.

Fig. 1.

Fig. 2.

Figs. 1 and 2.—Anterior and lateral views before operation.

Two thousand c.c. of whole blood was administered prophylactically during the three-hour operation. The lowest blood pressure recorded was 78/48. This occurred during the period of time when the patient was being repositioned into the supine position for closure of the incision. A prompt response of blood pressure followed cessation of manipulation of the patient (Fig. 3).

The patient reacted very soon following her return from the operating room and a mild elevation of blood pressure was noted during the early afternoon (Fig. 4). Six hours following completion of the operation a sudden decline in blood pressure with a very slight elevation in pulse rate was noted. Intravenous fluids were replaced with 500 c.c. of whole blood which was administered under pressure and 1 minim of 1:1,000 epinephrine was administered intravenously. The response of the blood pressure was satisfactory and there was no further difficulty with hypotension or elevation of pulse rate. At no time did the patient complain of syncope, nor was there evidence of intra-abdominal hemorrhage or other apparent cause for this abrupt lowering; the patient was never considered to have been in serious difficulty.

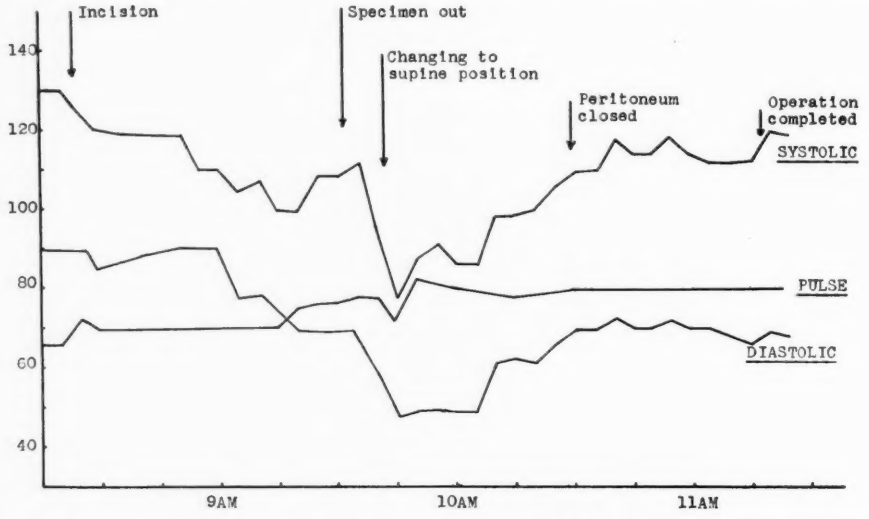

Fig. 3.—Shows systolic and diastolic blood pressure and pulse rate during operation.

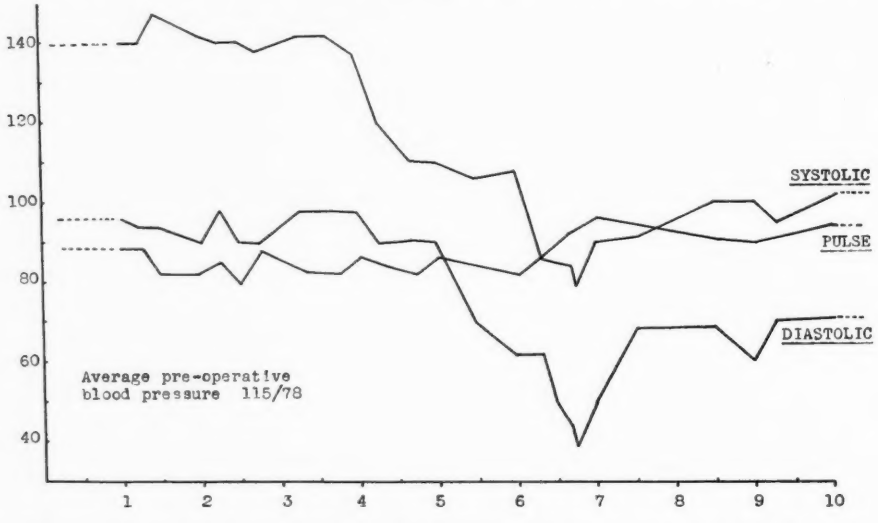

Fig. 4.—Shows systolic and diastolic blood pressure and pulse rate for the first ten postoperative hours.

The remainder of the postoperative course was uneventful. The patient was out of bed on the fifth postoperative day, and walking on the ninth postoperative day (Fig. 5). This delay in ambulation was due to the fact that she had not walked for some four months and physical therapy was necessary to strengthen the musculature of the lower extremities.

When checked postoperatively, in February, 1953, the patient was feeling well and had no complaints. Again, in May, 1953, she was doing well, weighed 184 pounds, and was normal on pelvic examination. By correspondence, in August, 1953, we learn that she is continuing to feel well and is carrying on activities as a field hand on a farm.

The ovarian tumor weighed 184 pounds. Approximately eight pounds (3,700 grams) of abdominal wall was excised. The patient weighed 319 pounds on the morning of the operation, and weighed 127 pounds upon returning from the operating room. The waist measurement was reduced from ninety to thirty-one and one-half inches. Pathological diagnosis: serous and pseudomucinous cystadenocarcinoma of the left ovary.

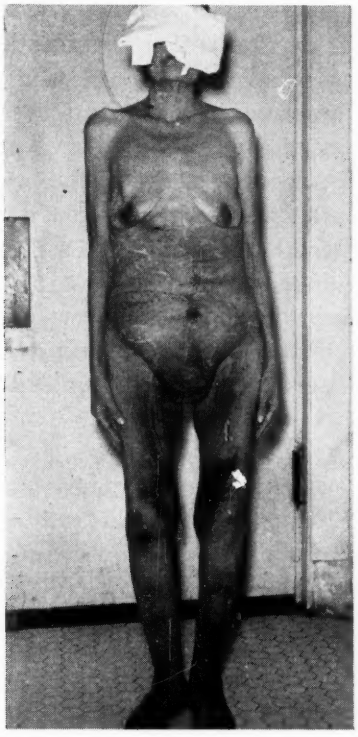

Fig. 5.—Patient before discharge.

Comment

From the study of the blood pressure and pulse rate in this case we see no evidence of splanchnic shock during the operation. There was a depression of the blood pressure to 78/48 which occurred during the interval in which the patient was being moved from the left lateral to the supine position, but this is not an unusual reaction. A similar fall in blood pressure which occasionally occurs upon the moving of a patient from the operating table onto a surgical carriage following the completion of an operation is well known. No essential change in pulse rate accompanied the fall in pressure and the pressure spontaneously responded to cessation of manipulation of the patient.

The postoperative course of the blood pressure shows a mild elevation persisting for about three hours with a gradual decline to normal levels. About five and one-half hours postoperatively there was a sudden fall in blood pressure

which is unexplained. Within a twenty-minute period the pressure fell from 108/64 to 80/40. This postoperative drop in blood pressure could possibly be attributed to a mild splanchnic shock, though it is by no means certain and there is no basis for stating that it is such. We are all quite familiar with such instances of unexplained depressions of blood pressure accompanied by only very slight changes in pulse rate following major surgery. The pressure responded without difficulty to 500 c.c. of whole blood under pressure and 1 minim of epinephrine intravenously; no further depression of blood pressure was noted.

Conclusions

Splanchnic shock due to a relatively rapid decrease in acute intra-abdominal pressure caused by removal of extremely large abdominal tumors is by no means constant in its appearance and is rather uncommon. When it does appear, it usually is manifested some hours following such a release in pressure, as a rule four to twenty-four hours later, and the use of "slow" decompression is poor prophylaxis. Instead, the most logical course of action seems to be the removal intact of such large tumors in order to face the possibilities of reaction with the patient in an optimum physical state.

With the use of whole blood and modern drugs this possibility has become secondary to the evils accompanying the drainage of any large ovarian tumor, and size alone should no longer be considered an indication for drainage rather than intact removal.

I wish to thank Dr. Willard R. Cooke for his guiding hand through the management of this case; Drs. Will H. Tinsley and C. R. S. MacKenzie for their assistance at the time of operation; and Dr. Victor W. Nowinski for his assistance in translation during the review of literature.

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Editorials

Nine Months After Kinsey

Nine months have elapsed since the long-awaited Kinsey report burst upon a waiting and apprehensive public. The results have been definitely short of revolutionary. The respect which the American woman has enjoyed appears to have suffered little impairment. The process of the liberalization of sexual mores has not been visibly accelerated. Rumor even has it that the sales of the report are falling far short of expectations. We can breathe a sigh of relief. *Sexual Behavior in the Human Female* is out and our society continues.

Yet it would be as great a mistake to underestimate the importance of Kinsey's work as it is to exaggerate it. It should give the gynecologist and obstetrician in particular cause for thought.

In the preparation of this Editorial more time has admittedly been devoted to the reviews of the book than to the original. For one thing, these condense what is evidently a long and sometimes tedious—as well as painstaking and conscientious—presentation of statistical data. The reviews reveal also the interpretation that may be placed upon Kinsey's original material by certain thoughtful readers. Finally, the list of reviewers indicates the type of person regarded, at least by the magazine editors, as competent to write on female sexual behavior. From this list the physician is nearly, and the gynecologist completely, absent.

Among eight or nine reviews of Kinsey's work, which have come to our attention in the last few months, the reviewers have had the following professions: "science writer," three; "anthropologist," two; "novelist," two; "psychologist," one; and "psychiatrist," one. Gynecology, the science of woman, is unrepresented. Neither this, nor any other medical journal so far as we know, was invited to the prepublication showing held in Indiana for the writers who might contribute reviews or comments.

This is perhaps more a criticism of the gynecologist than of Kinsey. The gynecologist is evidently not regarded as one informed on the subject of sexual behavior in the female. This view is probably correct, but it is not clear why this should be true or whether it ought to be so. The preoccupation of the obstetrician and gynecologist with the solution of organic problems is a partial explanation. Furthermore, the need that the woman should confide her organic complaints to the physician has required that she be protected against gratuitous intrusion upon other more intimate problems. We may well ask ourselves, however, whether the solution of many of the functional

complaints which come to the gynecologist may not now require an understanding of the background which Kinsey has supplied or else the reference of cases with such problems to practitioners of a different discipline.

With this confession of the deficiencies in the gynecologist's awareness of this subject, there remains an opportunity to submit certain, still unsolicited, comments upon the Kinsey report from the gynecologist's point of view. In the thousands of pages of comment already written it is hardly possible that anything remains that has not yet been referred to. However, the physician's viewpoint, characterized perhaps by a belief in the existence of a *pathology* for all living processes and a bias in favor of *therapy* as distinct from simple observation, may not have been fully heard.

Many critics, shocked by the statistics, have questioned the validity of Kinsey's sample. This appears a weak basis for criticism. In the first place, no one else has a series comparable in size nor is there much prospect of a similar series being collected in the near future. Furthermore, even if the figures for many of the items were cut in half or to a quarter the results would still be shocking to many moral, and indeed esthetic, sensibilities.

The attack upon Kinsey and upon the comments of some of his interpreters is to point out first that he has apparently confused *morality* with *prevalence* or indeed that he has equated the two. It is as though a social scientist, surveying the slums of a great city, concluded that since men seem to have chosen to live in tenements with inadequate plumbing this is the normal way to live. The physician in particular is entirely familiar with situations in which pathology may be the common lot of the majority of a population.

Related to this tacit elimination of pathology is Kinsey's segregation of physiology from the remainder of the text and his apparent assumption that manifestations of sexual behavior are isolated phenomena incapable of producing physiological derangement. Kinsey in appearing to give answers has at least succeeded in formulating certain questions. Within the now demonstrated spectrum of human sexual behavior the whole problem remains of determining what is normal, at least in the physician's sense, and what may strain the delicate mechanisms of vascular and autonomic function, not to mention psychological and social equilibria. The physician is familiar with a vast pathology dependent on alimentary habits. Is it reasonable to underestimate the possibilities of unphysiological sexual behavior or to overlook the risk of temporary or permanent ill effects? The check to "freer sexual mores" may not be "morality" but physiological limitations.

Finally, Kinsey has not considered reproduction, the biological objective of sexual activity. Probably Kinsey would point out that his work was already enormous and this additional aspect was not part of the assignment he had given himself. This would be a partial defense, but it is a serious step for any society to take when in its thinking it separates too far the related functions of sex and reproduction.

In spite of these serious reservations, it appears that the gynecologist must know more about *Sexual Behavior in the Human Female*. Probably the book

should not be on the practitioner's desk beside his *Operative Gynecology* and his *Essentials of Obstetrics*. It should, however, contribute to the basic knowledge of the gynecologist or obstetrician dealing with the complaints of patients that seem to have no organic basis. It should surely be the duty of some few investigators to attempt to relate certain of the Kinsey data to a variety of physiological disturbances, and perhaps to some organic lesions whose etiology and therapy remain yet undetermined.

H. C. T.

Kosmak Festschrift

The July JOURNAL will be devoted to articles written in honor of Dr. George Kosmak, who was editor of the JOURNAL through the last three decades when medical knowledge was advancing rapidly. Obstetrics and gynecology became a well-established specialty in the United States during this period, an accomplishment to which Dr. Kosmak contributed to no small extent.

All of the articles for the July JOURNAL were written on invitation, some by the colleagues of Dr. Kosmak's years of activity, many by present-day leaders of the specialty in America, a few by outstanding persons from abroad. Articles on most of the important aspects of obstetrics and gynecology today will be included.

The Editors

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Review of New Books*

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Human Embryology. By Bradley M. Patten, M.D., Professor of Anatomy, University of Michigan. 798 pages with 453 illustrations. Second edition, New York, 1953, Blakiston Company. $12.00.

The second edition of *Human Embryology* includes revision of much of the subject matter. Extensive changes have been made in two fields. The first is the development of the early human ova and embryos and human implantation. The author has justly credited many of the advances to the brilliant work of Drs. Hertig and Rock and has included several of their illustrations. The second is the production of congenital defects in the cardiovascular system. Recent progress in corrective surgery of these anomalies has stimulated the author to expand the material in this field.

As in the first edition, the text has been written to serve as a foundation for the understanding of other medical subjects, in particular, congenital malformations. Emphasis has also been given to the later stages of development of organ systems in order to aid the student in his study of gross and microscopic anatomy.

The book is very readable. The author has continued his clear, simple style of writing. He has added to the many illustrations present in the first edition, in recognition of their value in the understanding of the interrelationships of different organ systems. He has included some of the magnificent illustrations from the *Contributions to Embryology* of the Carnegie Institution.

In this edition the author has added to the high caliber of his first edition. It should make the book valuable to the medical student and profession.

The Practice of Balanced Anesthesia. By Sylvan M. Shane, D.D.S. 196 pages with 12 illustrations, Baltimore, 1953, Lowry and Volz. $5.75.

The author of this book is a dentist and a controversial figure among anesthetists in this country and abroad. However, there will be few anesthesiologists who will criticize the anesthetic principles given in this treatise.

This book is timely. Open drop ether is no longer the safest anesthetic. We are in the era of muscle relaxants and the endotracheal administration of multiple anesthetic agents to achieve light and safe anesthesia. The technique for balanced anesthesia is clearly described and amply illustrated in this book. Specifically, the author advocates a "balanced mixture" for anesthesia consisting of a barbiturate induction and an endotracheal mixture of 10 per cent cyclopropane, 40 to 45 per cent oxygen, and 45 per cent nitrous oxide with or without muscle relaxants. The modifications of this technique to suit pediatric and geriatric patients are emphasized. Preoperative medication and anesthetic emergencies are adequately covered.

*The Advisory Committee on Policy has agreed that most book reviews need not be signed.

Thirteen pages are devoted to obstetrical anesthesia. This is a minor section of the book; however, most of the major problems of obstetrical anesthesia are mentioned. The "balanced mixture" is advocated for the obstetrical patient. In cases where systemic anesthesia is required in obstetrics, the technique of Shane can be recommended.

An interesting section of the book is devoted to veterinary anesthesia and to the historical high lights of anesthesia.

This book can be enjoyed by any physician interested in anesthesia; but the techniques of anesthesia which are described and illustrated by the author should be employed only by the anesthesiologist.

Diseases of Women. By Robert James Crossen, A.B., M.D., F.A.C.S. Tenth edition, 935 pages with 990 illustrations. St. Louis, 1953, The C. V. Mosby Company. $18.50.

When the late Dr. Harry S. Crossen published his first edition of *Diseases of Women* in 1907, he established a tradition in the field of gynecological literature. Each subsequent edition was revised to keep abreast of progress in gynecology. In this, the tenth edition, Dr. Robert J. Crossen carries on the rich tradition of his predecessor. For this volume is not a mere compendium of the latest discoveries and advances. Rather, it is a comprehensive and well-organized presentation of current thought and practice.

The customary section on anatomy and physiology is not only very complete and well illustrated but unusually lucid and readable. Dr. Willard Allen has contributed a concise review of the endocrine relations concerned in the ovarian cycle that clarifies many of the present concepts of the sex hormones.

Although the author stresses in his preface the importance of the psychosomatic aspects of gynecology, he fails to develop this thesis in the otherwise complete section devoted to gynecologic examinations and diagnosis. Not only are the routine examinations aptly described and illustrated, but also special studies such as vaginal smears, culdoscopy, tubal insufflation, and so forth. For a more detailed analysis of these various procedures, there are ample references to the original publications.

In the remaining sections of the book, there is a thorough presentation of the various gynecological diseases affecting each organ. The etiology, pathology, symptoms, diagnosis, and treatment of the individual conditions are described. Some discussions are more complete than others, but there are rather complete references for all. Dr. A. N. Arneson has contributed a worth-while review on the prineiples of radiation therapy of cervical cancer. In the chapter relating to displacements of the uterus, the reader is treated to a graphic presentation of the role and use of different types of pessaries. Few currently trained gynecologists have any familiarity with these therapeutic tools, so important in the past. Such miscellaneous conditions as sterility, sexual disturbances, and climacteric are briefly discussed in the closing chapters.

The publishers of *Diseases of Women* are to be congratulated for their refreshing and modern format. In general, they have succeeded by color plates, line drawings, pen sketches, and black and white prints, in composing a well-illustrated book. In presenting a *readable book,* the author is to be complimented on achieving a success that has escaped many of his medical contemporaries. Although the specialists might desire more complete information on a particular topic, Dr. Crossen has followed the tradition of his predecessor in publishing a very comprehensive and valuable volume not only for the student but also for the practicing gynecologist.

Sex: Methods and Manners. By Louis Berg, M.D., and Robert Street. 249 pages with 2 illustrations. New York, 1953, The McBride Company. $3.50.

As indicated in the title, this book for the average layman does not concern itself with the medical aspects of reproduction, but describes in minute detail the techniques of lovemaking and bedroom manners. The authors' style is literate and straighforward, and very

little is left to the imagination. The final chapter of the book is devoted to a discussion of the happy marriage, together with the problems that often beset it.

The book may be recommended to those who would like to advance themselves in sexual techniques, as well as to the intelligent newlyweds seeking such information from a book.

Diseases of Women. By Frederick Roques, M.D., Beattie, and Wrigley. 480 pages with 178 illustrations. Ninth edition, London, 1953, Edward Arnold & Co. $6.50.

As with the previous editions of *Diseases of Women*, the editors through ten contributors have endeavored to deliver to the medical student and to the young practitioner the principles of gynecology in a concise and comprehensible manner.

The text is small and quickly read, and yet all aspects are adequately covered. It begins with a brief review of the anatomy, embryology, and physiology of the female pelvic organs, and continues on to gynecologic diagnosis, technique, and treatment.

The authors should be congratulated for the informative but concise manner in which they have presented such topics as endocrine function, backache, sterility, genital prolapse, and for their review of the common gynecologic operations which are usually difficult for students to understand. Ample illustrations are included throughout all chapters.

Such a controversial subject as the treatment of carcinoma of the cervix is presented completely without bias and at the same time sufficiently covered. The differentiation of lichenoid lesions of the vulva from true leukoplakia vulvae is emphasized.

The English contributors, however, appear to be more conservative than we in the treatment of chronic pelvic inflammatory disease.

There is no doubt in the reviewer's mind that this book would be a valuable aid to beginners in the field of gynecology.

Eden and Holland's Manual of Obstetrics. By Alan Brews, M.D., M.S., M.R.C.P., F.R.C.S., F.R.C.O.G. Tenth edition, 812 pages with 375 illustrations. London, 1953, J. & A. Churchill, Ltd. 52s. 6d.

This tenth edition of *Eden and Holland's Manual of Obstetrics* by Dr. Brews is intended primarily as a textbook for the medical student and the physician engaged in general practice. The material is well organized and begins with a discussion of the menstrual cycle and proceeds to the fertilization of the ovum, followed by a rather complete summary of the development of the fetus and placenta. Dr. Brews then follows the usual textbook format of normal and abnormal pregnancies, labor and its complications, and the puerperium. There is an additional chapter on the care of the newborn and methods of resuscitation. The book concludes with a presentation of the indications and techniques of the various obstetrical operations.

The author is rather liberal in his indications for therapeutic abortions, listing such things as some cases of hyperemesis gravidarum, multiple sclerosis, and pulmonary tuberculosis. He also advocated cesarean section in certain patients with severe cardiac disease without sufficient obstetrical indications.

In general, too little attention is paid to some of the controversial aspects of obstetrics such as hypotensive drugs in the treatment of toxemia, the use of extraperitoneal cesarean section, estrogen therapy for the pregnant diabetic patient, and conduction anesthesia.

The reproduction of the illustrations is not the best, and the quality of the paper used varies considerably from place to place. This, of course, places a burden upon the reader.

This latest edition of a standard British textbook is a valuable aid for the medical student but will not greatly benefit the specialist.

Praktische Geburtshilfe. By Prof. Dr. W. Pschyrembel, from the Woman's Clinic of the City Hospital of Berlin-Friedrichshain. Third edition, 657 pages with 457 illustrations. Berlin, 1953, Walter De Gruyter and Co. DM 28.

This textbook is just what the name implies. Every page is crammed with practical advice, suggestions, and aids to the general practitioner and student. The material is arranged

in a most interesting manner. Basic principles are printed in bold-faced type and surrounded by black borders. The book is arranged in outline form, much as a student might arrange his notes when studying for an examination. Moreover, there are outline summaries at the end of each section and parallel marginal lines to draw attention to statements of unusual importance.

In common with many recent German works, the book lays considerable emphasis upon external pelvimetry and upon vaginal manipulations. Roentgen pelvimetry is brushed aside. In fact, the statement is made that x-ray diagnosis should be undertaken only in unusual situations because of danger to the endocrine glands of mother and fetus. The reviewer would disagree that the retained placenta should be allowed to remain in situ for one to two hours before measures are taken to remove it.

The book is illustrated with numerous diagrams and line drawings, all of which are easily understood.

Altogether, this is a most refreshing obstetric manual. Although it contains nothing new, it should be of considerable service to those for whom it was written.

The Digestive Tract in Roentgenology. By Jacob Buckstein, M.D. Second edition, two volumes with 1,534 illustrations in 897 figures. Philadelphia, 1953, J. B. Lippincott Company. $30.00.

The author must undoubtedly be highly commended for such a comprehensive study of the digestive tract from a roentgenological aspect. The material is extremely extensive and deals with practically every lesion, disease, or condition conceived in medicine.

Each aspect of the digestive tract is clearly and completely brought forward and described. Clinical case reports are given in conjunction with every lesion presented. Various technical procedures are given which are of inestimable aid to the roentgenologist in determining the presence of extremely rare conditions, particularly some congenital abnormalities, which procedures ordinarily are not used routinely. The majority of bizarre lesions have been verified by operation or autopsy.

The normal variations of each aspect of the digestive tract are clearly described and illustrated. The pathological lesions and congenital abnormalities are demonstrated and described with numerous illustrations and correlated with clinical cases which are of great value to the roentgenologist, surgeon, internist, gastroenterologist, and proctologist.

The findings before and after operation are well demonstrated. This is also true of those cases which came to autopsy.

The illustrations of the various pathological lesions are quite clear, which incidentally has been one of the "drawbacks" in demonstrating pathological conditions on paper. The process of transposing the image of the film to paper has been unsatisfactory at times, but not in this work.

Numerous microscopic illustrations are given in black and white. This of course definitely detracts from the effectiveness of illustration of the lesions. Colored illustrations would undoubtedly impress the various microscopic pathological lesions more firmly upon the mind of the reader.

The author's vast experience is remarkably manifested by such a complete and comprehensive presentation. In the opinion of the reviewer, this latest production of Dr. Jacob Buckstein is a "must" for the libraries of roentgenologists, surgeons, gastroenterologists, internists, and proctologists, and probably for many others.

The Hypertensive Disorders of Pregnancy. By Ernest W. Page, M.D. 120 pages with 2 figures and 5 tables. Springfield, Ill., 1953, Charles C Thomas. $3.75.

The introduction deals briefly with the development of toxemia classifications and definitions. Chapter I presents the toxemic patient as seen by the physician, from early in pregnancy through years of follow-up (or autopsy if she dies). A vast amount of integrated information is compressed into 46 pages of lucid writing. One of the amusing

features is a table of premiums which selected groups of women might be charged for insurance against toxemia. This table emphasizes factors which predispose to the development of pre-eclampsia and gives an estimate of their relative weights. The management of the patients and the treatment of their complications are succinctly outlined.

Chapter II summarizes in 32 pages some of the physiological and chemical changes of normal and toxic pregnancies. Subjects discussed include the circulation, renal function, water and electrolyte balance, some of the hormones, and blood chemistry.

Chapter III considers the etiology of toxemia. As the author writes, "No attempt will be made to avoid favoring our own theory . . . slanting this presentation with prejudice could only be avoided by writing a lengthy, heavily documented and uncritical volume." The theory is that placental ischemia is the precipitating cause of toxemia. Page's differentiation of predisposing factors, precipitating factor ("cause"), mediators, and secondary manifestations should be read by anyone interested in toxemia (or other disease). There are hundreds of papers in the literature which have confused the issue by regarding predisposing factors as "causes." Even secondary manifestations (*e.g.*, vasoconstriction) have been regarded as fundamental.

Extensive clinical and physiological observations are marshalled in support of the author's theory and many diverse data are correlated.

Certainly no one could write a book without making some statements unacceptable to a reviewer. Among several which this reviewer does not believe are: that 90 per cent of pre-eclamptic patients show rapid weight gain as a first sign; that salt can be "washed out" by water diuresis; that the blood uric acid level gives an indication of the severity of the toxemia; that "vascular constriction leads to tissue hypoxia and contributes to edema formation." It is doubtful whether Page himself believes the last statement, although it appears on page 106.

In a picayune vein, the editorial proofreader missed an undue number of typographical errors and inconsistencies—"posterior pituitary," for instance, is rendered four different ways.

As anyone knowing Page's work might expect, this is an excellent, concise, and stimulating book which will be of value to the physician doing some obstetrics, to the obstetrician, and to the specialist in toxemia. Highly recommended.

Sexual Behavior in the Human Female. By Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, and Paul H. Gebhard, from the Institute for Sex Research, Indiana University, Bloomington, Ind. 842 pages with 179 tables and 155 figures. Philadelphia and London, 1953, W. B. Saunders Company. $8.00.

Dr. Alfred C. Kinsey, who "had been at work for several years collecting sex histories of persons in all walks of life, and in gaining acquaintance with sexual habits and customs, and with the social, commercial, and criminal aspects of sex in the United States,"* obtained in 1941 from the Committee for Research in Problems of Sex of the National Research Council "a small grant" ($1600). . . . "to aid in collecting and analyzing histories." Increasing financial support was given by the Committee until, in 1948, further grants were made unnecessary by the abundant royalties from the sale of the book entitled *Sexual Behavior in the Human Male.* All such profits are assigned to the Institute for Sex Research of Indiana University, whence comes the second volume here under discussion.

That the Committee for Research in Problems of Sex, made up of illustrious scientific personages, should eventually endow Dr. Kinsey with its considerable prestige is not surprising. This group was organized in 1922 by the National Research Council in response to the following resolution, which is a summary of the conclusions of a conference of learned men held in 1921 under the auspices of the Council and the chairmanship of Dr. Walter B. Cannon of the Medical School of Harvard University:

*Aberle, Sophie D., and Corner, George W.: Twenty-Five Years of Sex Research. History of the National Research Council Committee for Research in Problems of Sex. 1922-1947. Philadelphia and London, 1953, W. B. Saunders Company.

"RESOLUTION: The impulses and activities associated with sex behavior and reproduction are fundamentally important for the welfare of the individual, the family, the community, the race. Nevertheless, the reports of personal experience are lacking and the relatively few data of observation have not been collected in serviceable form. Under circumstances where we should have knowledge and intelligence, we are ignorant. To a large degree, our ignorance is due to enshrouding of sex relations in a fog of mystery, reticence and shame. Attitudes toward the subject have been fixed by moral teaching, medical instruction and social propaganda, all based on only a slight foundation of well-established fact. In the presence of this secrecy and prejudice scientific investigation would be difficult. The Committee is convinced, however, that with the use of methods employed in physiology, psychology, anthropology, and related sciences, problems of sex behavior can be subjected to scientific examination. In order to eliminate any suggestion that such inquiry is undertaken for purposes of propaganda, it should be sponsored by a body of investigators whose disinterested devotion to science is well recognized. For these various reasons, the Committee recommends that the National Research Council be advised to organize and foster an investigation into the problems of sex." (Pages 12-13.)

In the first 21 pages of this book the authors convincingly elaborate on the scope, the need, and the justification of their studies and of the publication of their results in such manner as to make them useful to the lay reader. Already too many commentators have manifested failure to read three significant, carefully worded paragraphs:

(In the following, from page 4, all but the first two italicizations are mine.)

"This is a study of sexual behavior in (*within*) certain groups of the human species, *Homo sapiens*. It is obviously not a study of the sexual behavior of all cultures and of all races of man. At its *best*, the present volume can *pretend* to report behavior which *may* be typical of *no more than a portion*, although probably not an inconsiderable portion, of the white females living *within* the boundaries of the United States. Neither the title of our first volume on the male, nor the title of this volume on the female, should be taken to imply that the authors are unaware of the diversity which exists in patterns of sexual behavior in other parts of the world."

Further, on page 537, we read:

"It is obvious, but it needs to be pointed out again, that no population of variant individuals can ever have their behavior characterized by any simple description. It is more nearly possible to write anatomic descriptions which cover a whole group of individuals, but physiologic functions are usually more variable than anatomic structures, and behavioral characters are still more variable than physiologic functions."

Also, on page 543, is the pointed statement:

"The sexual history of each individual represents a unique combination of . . . variables. There is little chance that such a combination has ever existed before, or ever will exist again. We have never found any individual who was a composite of all the averages on all of the aspects of sexual response and overt activity which we have analyzed in the present volume. This is the most important fact which we can report on the sexual histories of the females who have contributed to the present study."

Chapters 2 and 3, comprising 75 pages, are devoted to an extremely detailed exposition of how and where the subject matter was obtained and of the methodology of statistical analysis. Then follow ten chapters (466 pages) of finely processed meat, the micronized carnality of 5,940 white females of the United States. Incidences of almost every manner and degree of sexuality are given for numerous categories, such as those of age, of social and marital position, of religious attitude, of educational background: an impressive example of truly scientific ardor in obtaining material as best one can, and also of a sincere attempt to utilize its full possibilities.

Few of the frequencies of this or that particular manifestation of sex will surprise many experienced gynecologists. Therefore, and also because of the futility of attempting within the bounds of space and accuracy to summarize such a plethora of numerical de-

tails, I quote no specific findings. But in these chapters there is much more than statistics, skillfully presented in luminous tables and graphs. Embellishing the flavorless figures are constantly recurring commentaries telling why in the opinion of the authors sexual behavior is found thus and so in this or that category. These profuse interpolations not only add immeasurably to the readability of the book but also rather clearly evince the seasoned apperceptions of these assertedly unprejudiced investigators. They who have ranged so widely and delved so deeply in sexuality would be less than human did they not for themselves synthesize their observations into explanations and theories; nor would they have approached their objective of educating the public in the actualities of sex were they to withhold completely their own expert conclusions from the facts as they found them.

Nowhere in the book, however, is there any overt defilement of their avowed objectivity by a compact explicit expression of the authors' concept of sex ethics; but between, sometimes even within, the lines of innumerable pages sadly this reader detects what appears to be either an utter incomprehension that Man is more than an amoral animal, or an incomprehensible moralistic flaccidity in one phase of their otherwise superb and avowed effort toward public welfare. Among seventeen casually noted similarly slanted passages appear the following two:

Page 327: (Italics are mine.) "Because of its emotional connotations, pre-marital coitus, like any other type of socio-sexual experience, may have long-range effects which are of considerable social significance. In socio-sexual contacts, individuals may *become acquainted* with each other, learn to *adjust physically and emotionally,* come to *understand* each other, and come to *appreciate* each other's qualities in a way which is not possible in any other type of social relationship. *Learning to respond emotionally* to a sexual partner *may contribute to the effectiveness* of one's other, nonsexual, social relationships."

Here, the authors strongly insinuate justification of pre-marital coitus by slyly or inadvertently garnishing one of its possible effects with such general desirabilities as are italicized by me. This passage, I think, states not what they found, but rather a possible misinterpretation by them of their objective data.

On page 483 is another likewise "loaded" paragraph:

"Condemnations of homosexual as well as some other types of sexual activity are based on the argument that they do not serve the *prime* function of sex, which is *interpreted* to be procreation, and in that sense represent a perversion of what is *taken* to be '*normal*' sexual behavior. It is contended that the general spread of homosexuality would threaten the existence of the human species, and that the integrity of the home and of the social organization could not be maintained if homosexual activity were not condemned by moral codes and public opinion and made punishable under the statute law. The argument ignored the fact that the existent mammalian species have managed to *survive*" (as if that were sufficient for human beings) "in spite of their widespread homosexual activity, and that sexual relations between males seem to be widespread in certain cultures (for instance, Moslem and Buddhist cultures) which are more seriously concerned with problems of overpopulation than they are with any threat of underpopulation. Interestingly enough these are also cultures in which the institution of the family is very strong." (Italics are mine.)

This paragraph appears in a discussion of "Social Significance of Homosexuality," which starts on page 476. As does the whole subchapter, it clearly connotes approval of this manner of sex expression, just as the section "Social Significance" (of pre-marital coitus), starting on page 326, implies, purposefully or not, esteem for this common behaviorism.

Even the science of biology must accord humanity to human beings. Humanity is differentiated from bestiality by its component of spirituality, which Webster says pertains to "moral feelings." To those who believe that western civilization surpasses others in the welfare of all, morality of sex is inseparable from monogamy. It is at least highly debatable that either homosexuality or pre-marital coitus conforms to or strengthens

monogamy. I think that authors do wrong repeatedly to give the impression that their objective findings substantiate the morality of these substitutes for monogamy. Their excellent detailed analysis of case histories certainly does not do this for me.

The first two sections of this tripartite volume, in spite of adverse criticism of expert statisticians, would fully justify a title such as *Sexual Behavior of 5,940 White American Females* and amply accord the authors illustrious eminence among social scientists. The last five chapters, comprising Part III, entitled "Comparisons of Female and Male," appreciably add to their scholarly stature, for herein, utilizing our limited available basic science, they lucidly expound—though frequently without proving—their theories of all-inclusive sex physiology; i.e., all inclusive except for the element of spirituality. This they either do not recognize as a factor in human psychology, or refuse to include for the needless fear that its implication would contaminate the purity of their "science."

These last chapters are respectively entitled: "Anatomy of Sexual Response and Orgasm"; "Physiology of Sexual Response and Orgasm"; "Psychologic Factors in Sexual Response"; "Neural Mechanisms of Sexual Response"; "Hormonal Factors in Sexual Response." I believe careful study of them should be added to the requirements for board accreditation at least in gynecology and obstetrics, and wish such requirement could be made retroactive for those already certified in these specialties.

Now many psychoanalysts, jurists, professional moralists, all clinicians and family-counselors-in-sex, pedogogues, and parents re-examine their doctrines and replenish their tools by only a few days' discriminating reading of the first two parts and careful study of Part III of this immensely instructive book. In size it is 9¼ by 6 inches wide and 1⅝ inches thick and weighs only 2½ pounds. It is securely bound and legibly printed with wide page margins for both pro- and con- notes. Its plenitude of references makes of it a bibliographic compendium. Its abundant citations of conflicting reports and views are a high tribute to the authors' impartial scholarship. The text is a literary achievement in integration of authorship as well as in pleasing style. Indiana University and the Committee for Research in Problems of Sex of the National Research Council, which, together, from first to last have sponsored these studies, can well feel proud of their product. The authors, collectively called "the Staff of the Institute for Sex Research, Indiana University," and individually named as Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, and Paul H. Gebhard, merit high acclaim for a very difficult job well done.

Prematurity, Congenital Malformation and Birth Injury—Proceedings. By Dr. I. E. Holt, Jr., Department of Pediatrics, New York University College of Medicine, Dr. Theodore Ingalls, Department of Epidemiology, Harvard University, and Dr. Louis M. Hellman, Department of Obstetrics and Gynecology, State University of New York College of Medicine at New York City. 255 pages. New York, 1953, published by the Association for the Aid of Crippled Children. $4.00.

Prematurity, congenital malformation and birth injury, their prevention and medical management constitute one of the major problems confronting obstetricians, pediatricians, and public health workers. Not only are these conditions, in the order mentioned, the leading causes of death in the first month of life but they are of even greater community importance from the point of view of the crippling defects which handicap many of the survivors. It is of significance that this conference was sponsored by the New York Association for Aid to Crippled Children.

Thirty papers were presented under the co-chairmanship of Dr. Emmet Holt, a pediatrician, Dr. Theodore Ingalls, an epidemiologist and public health worker, and Dr. Louis Hellman, an obstetrician. These papers, presented by experts in their respective fields, give the reader a bird's-eye view of much of the recent research in these fields. Some of the material presented is highly provocative; in the field of prematurity those papers relating to the prevention of prematurity and to the maturation of enzyme systems seem of particular importance.

The problem of evaluating factors concerned in the production of congenital malformation is discussed in eight papers and is approached from three points of view—laboratory, clinical, and statistical. The relationship between birth injury and prematurity is pointed out in a paper entitled, "Mass Study of Reproductive Wastage."

The seven papers presented under the general heading of birth injury contain a large number of data. They should serve as a stimulus to finding a pathway through the virtually uncharted field of anoxia and its biochemical and physiopathologic manifestations.

Pregnancy Wastage. By Earl T. Engle, M.D., 266 pages with 82 illustrations. Springfield, Ill., 1953, Charles C Thomas. $8.50.

This small book contains much interesting material which is the result of the proceedings of a conference held in 1951 and sponsored by the Committee on Human Reproduction of the National Research Council in behalf of the National Committee on Maternal Health. The book was edited by Dr. Earl Engle and has an introduction by him which briefly emphasizes the subject of the conference. Dr. Engle states that while the human race has been singularly adept at reproducing itself, there is no known measure of the proportion of conceptions which succumb or the factors responsible for this wastage.

The session chairmen were Drs. Rock, Eastman, D'Esopo, and Hertig. There were 15 major topics covered, the most outstanding of which were, in the opinion of this author, those by Dr. George Corner on Early Abnormal Embryos in the Rhesus Monkey, Dr. Edward Hughes on the Role of the Endometrium in Implantation and Fetal Growth, Dr. Joseph Jailer on ACTH and Cortisone in Pregnancy, Dr. Christopher Tietze on the Introduction to the Statistics of Abortion, and Dr. Arpad Csapo on Contractility of the Uterus. While these particular topics have been singled out for mention, it would be unfair not to state that the remainder of the book contains much valuable and pertinent information on the subject of pregnancy wastage which cannot be obtained easily from any other source. The discussion of the various topics was particularly timely and in many cases as illuminating as the original presentation.

It is unfortunate that the reporting of these conferences takes so long to get into print. In this case, a matter of two years seems to have elapsed before much of this material became available. It is also unfortunate that the data presented by the discussers of the various topics are not more fully illustrated.

In summary, this small volume is of considerable value to any student of the subject of pregnancy wastage.

Clinical Endocrinology. By Karl Paschkis, M.D., Abraham Rackoff, M.D., and Abraham Cantarow, M.D. 768 pages with 254 illustrations. New York, 1954, Hoeber-Harper. $16.00.

This volume represents the combined efforts of an Associate Professor of Medicine, a Clinical Professor of Obstetric and Gynecologic Endocrinology, and a Professor of Biochemistry. All have been nationally known for their interest in endocrinology. The work is intensely interesting and reads more like a novel than a reference book. The data and references are up to date. The book itself is divided into 12 sections. Ten of these relate to specific endocrine glands and their disorders, such as the pituitary, the thyroid, the adrenal cortex, the adrenal medulla, the ovaries, the testes, the pancreas, and the parathyroid. Included as an endocrine gland, and quite correctly, is the placenta. In addition, there is a section on obesity and one on methods and materials. The sections are presented in an orderly manner, beginning with the anatomy and physiology of the various glands or parts of glands under discussion. There then follow discussions of malfunction usually divided into hyper- and hypofunction of the various compartments of the organ discussed. Specific diseases and various syndromes of malfunction are described and treatment and theory of treatment given. In addition, the interrelationships with other glands are thoroughly discussed. References are given at the end of each section. The volume is

extensively illustrated and the paper excellent. For the most part, the reproductions are good; however, occasionally the charts, as in Figure 136, are unreadable. In addition, there are occasional photomicrographs which are extremely poor and detract from what is otherwise a splendid piece of craftsmanship. This volume, as are many similar texts on endocrinology, is confusing when it speaks of biological methods of assay. In particular, in dealing with the pituitary and the placental hormones, there is no attempt made to translate data into standard units of measurement. This makes a difficult situation for the student.

The section on procedure is superficial and not given in sufficient detail to enable the reader to perform many of the tests indicated. However, the references are included, and it was perhaps the purpose of the authors merely to give an indication as to how these tests were done with their resultant values.

Criticisms leveled at this volume are minor in nature. It appears to this reviewer to be one of the outstanding contributions to clinical endocrinology and one which can certainly be read with pleasure and profit.

Correspondence

Answer to Dr. Morgan on Intrapartum Hemorrhage

To the Editors:

Dr. J. E. Morgan's excellent comments on my article on "Intrapartum Hemorrhage," in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY **66**: 902, 1953, are most interesting and instructive. His classification of bleeding according to its origin is correct and of prognostic value.

Dr. Morgan's observations on immediate expulsion of the intact placenta are illuminating, although I am not certain that I agree with all of his conclusions. Expulsion of the placenta and the concomitant closure of the large blood sinuses change the circulation so that the same conditions no longer prevail. On the other hand, fetal anemia found in cases in which a portion of the placenta has separated is considered to indicate the possibility of fetal as well as maternal hemorrhage. Laceration of the cord may mean injury to the umbilical vein or arteries with loss of fetal blood.

I wish to thank Dr. Morgan for his interest. This type of constructive comment stimulates medical progress.

HARRY S. FIST, M.D.

8712 WILSHIRE BLVD.
BEVERLY HILLS, CALIF.
DEC. 28, 1953.

Observations in India

To the Editors:

The Editors of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY deserve commendation for the inauguration of an ear-cupping policy which denotes that added consideration and recognition will be given to manuscripts originating from abroad. There is a lamentably frequent recourse to "variation" when some seek to explain the deviations from an accepted standard or behavior. Such variations and exceptions thus become the refuge of the witless and the answer to prayer when more critical explanations are wanting. Yet, the fact is, variations do exist and continue to confound us.

While the representatives of *Homo sapiens* have many features in common, different ethnic groups possess qualities and characteristics unique unto themselves. When one speaks of "normal," one should immediately ask, "Normal to what standard?" What may be regarded as quite normal for one segment of the population is not necessarily normal for others. Statistics derived from a mixed population may be significant only if a considerable number of samples are included. At best they apply only to a chosen few selected from genetically heterogeneous types. Familiarity with racial or genetic backgrounds of patients should frequently give the true explanation of their condition or response to therapy.

Observations made in a community such as is represented in Southern India where the population is more homogeneous, immobile—inbred as it were—than applies generally to the United States fortify the thesis that the permissibility of variations is oftentimes abused. At the Government of Madras Maternity and Children's Hospital where some 9,000 deliveries occur yearly, there are offered exellent facilities for studying large numbers representative of a relatively pure racial type.

Here the incidence of Rh-negative mothers averages 1 to 2 per cent. Here also the incidence of a depressed hemoglobin is so prevalent that 65 per cent is regarded as normal or at least not worthy of special note or treatment. Only 44 out of 727 consecutive ma-

ternity patients were noted to have a hemoglobin above 80 per cent. With the subjugation of infection and acute hemorrhage, idiopathic anemia of pregnancy shares with eclampsia the distinction of being a major cause of maternal mortality (20 per cent).

Even among ostensibly healthy pregnant women the urea clearance in a long series of unselected cases has been found to range from 15 to 20 per cent. One would judge from this that the Indian kidney is less efficient than its American counterpart. Furthermore, Indian women may appear to be able to handle certain manifestations of the eclampsia better than do their Western sisters. Here patients may have as many as 25 convulsions, with blood uric acid levels above 12 mg. per cent, without unfavorable outcome.

The dimensional description of the typical normal pelvis in American textbooks makes adequate provision for an average-sized fetus in a mixed American population. But in Madras where some 25 per cent of the newborn infants weigh less than 5 pounds, a smaller pelvis than is described in the American literature would appear to be normal.

That differences in hereditary backgrounds may explain differences in incidence and reaction to disease and response to therapy, at least in the experimental animal, has been demonstrated by Dr. Khanolkar of the Canadian Cancer Research Institute, and others. Certain long-pedigreed strains of mice will yield a predictable incidence of carcinoma as a result of a particular experimental regimen of estrogen administration, while other pure strains are quite immune to the same procedures.

Some 95 to 97 per cent of the Indian women can and do breast feed their infants. Possibly this deviation from the condition prevailing in many parts of America is referable to a different genetic composition of these people. But one may more properly wonder if the alleged inability of many American women to nurse their babies is not a cultural rather than a physical or physiological attribute.

Among the Hindus, circumcision is not practiced, but it is among the Moslems. Yet there is apparently no difference in the incidence of phimosis or of penile carcinoma between these two groups. Furthermore, carcinoma of the cervix is also about equally divided between Hindus and Moslems. Such observations and comments offer support to the admonition that one should be sparing with praise of superficial conclusions based on acquaintance with only a limited group of individuals. Interviews or studies even of 5,000 selected women hardly qualify one to speak for all womankind.

W. T. Pommerenke, M.D.

Strong Memorial Hospital
Rochester, N. Y.
March 18, 1954

Items

American Board of Obstetrics and Gynecology

Candidates are urged to make application for certification some time in August or September of 1954, for examinations held in 1955. The deadline date for the receipt of new applications and requests for reopening of application is Oct. 1, 1954.

It is drawn to the attention of candidates applying for admission to the Part I examinations that they are required to submit a list of all patients for whom they have been solely responsible admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application.

Requests for Applications for Appraisal of Incomplete Training, Applications for Certification, current Board Bulletins, and Preceptorship or Supplemental Training Forms should be made to:

ROBERT L. FAULKNER, M.D., SECRETARY
2105 Adelbert Road
Cleveland 6, Ohio

Assises Françaises de Gynécologie

The Assises Françaises de Gynécologie will meet in Paris from July 19 to 22, 1954. The subject for discussion is "Treatment of Genital Prolapse." Those interested in attending this meeting should write to the Secretary, Dr. Robert Senechal, 31 rue Raynouard, Paris (16^{me}), France, before June 15, 1954.

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